

Multifunctional Proteins in Tumorigenesis: Aminoacyl-tRNA Synthetases and Translational Components

Sang Won Lee¹, Young Sun Kang² and Sunghoon Kim^{3,*}

¹Department of Science and Technology Education for Life, Seoul National University of Education, 1650, Seocho-dong, Seocho-gu, Seoul 137-742, Korea; ²Department of Biomedical Science & Technology Institute of Biomedical Science & Technology (IBST), Konkuk University, 1 Hwayang-dong, Kwangjin-gu, Seoul 143-701 Korea and ³National Creative Research Initiatives Center for ARS Network, College of Pharmacy, Seoul National University, San 56-1, Shillim-dong, Kwanak-gu, Seoul 151-742, Korea

Abstract: Since translation is a central process in all living organisms, the components of translational machinery containing aminoacyl-tRNA synthetases, initiation, elongation, and releasing factors and ribosomal proteins have been considered as housekeepers of the cells. While these components are necessary for translational control, many of them have been found also to be involved in the control of cell fate through the diverse functions that are seemingly unrelated to protein synthesis. Also, there are several lines of evidence, suggesting the association of eukaryotic translational components with cancer development although the exact underlying mechanisms still await further investigation. Here we address the involvement of the translational components in the cell transformation and malignant phenotypes and the relationship of the deregulation of translational control of a wide range of cancers to provide systematic view on the association of translational components with cancers.

Key Words: Aminoacyl-tRNA synthetase, ribosomal protein, translation initiation factor, translation elongation factor, translation releasing factor, translation, cell transformation, malignant phenotype, multi-functionality.

INTRODUCTION

Translation is one of the most complex biological processes, involving diverse protein factors and enzymes as well as three major species of RNA. In eukaryotic systems, this process consists of initiation, elongation and termination steps, and these steps are controlled by multisubunit protein complexes that are comprised of aminoacyl-tRNA synthetases (ARSs), initiation factors (eIFs), elongation factors (eEFs), releasing factors (eRFs), and ribosomal proteins (RPs) (Table 1). Among these steps, the initiation in mammalian cells is the most complex step involving a set of eIFs and has been considered as the major target site for the control of translation and cell proliferation (Pestova and Hellen, 2001). However, many recent studies suggested that other translational factors such as ARSs, eEFs, eRFs, and RPs also could be important players in the regulation of cell proliferation (Ejiri *et al.*, 2002; Lee *et al.*, 2004; Ruggero and Pandolfi, 2003; Thornton *et al.*, 2003). Translational control is required for the fine-tuning of protein levels during cell proliferation and differentiation, the adaptation to cellular stress, and spatial or temporal regulation of protein expression (Hake and Richter, 1997; Ibbá and Soll, 1999).

Although translational components have not been the primary area of interest in the studies of cancer, there are accumulating data implicating the possible association of translational factors with cell proliferation and cancer formation (Caraglia *et al.*, 2000; Clemens and Bommer, 1999; Fingar *et al.*, 2004; Holland, 2004; Meric and Hunt, 2002; Rajasekhar and Holland, 2004). In fact, changes in the expression pattern of translational components can lead to several changes in tumour cells such as an increase in the overall rate of protein synthesis and/or overexpression of specific proteins involved in cell growth and proliferation (De Benedetti and Graff, 2004; Meric and Hunt, 2002; Rajasekhar and Holland, 2004; Rhoads, 1999). Three main alterations at the translational level appear to be associated with cancer formation: variations in mRNA sequences affecting translational efficiency, changes in the expression or availability of the translational components, and activation of translation through aberrantly activated signal transduction

pathways. The first alteration affects the translation of an individual mRNA that may play a role in carcinogenesis. The second and third alterations can lead to more global changes such as an increase in the overall rate of protein synthesis and translational activation of several mRNA species (Meric and Hunt, 2002). Although many of translational components are closely associated with cancer formation, only a limited number of them have been explored as biomarkers for cancer diagnosis or therapeutic targets for anticancer agents (Wiesenthal *et al.*, 2006). In this review, we collected the translational factors that are thought to be associated with cancer formation, and classified them according to their roles in protein synthesis and related cancers to see their functional and pathological linkages in systematic manner.

AMINOACYL-tRNA SYNTHETASES

Aminoacyl-tRNA synthetases (ARSs) catalyze the ligation of specific amino acids to their cognate tRNAs during protein synthesis, and their catalytic activities represent essential role in maintenance of cell viability. During their long evolutionary history, some ARSs acquired additional functions including regulation of transcription and translation, RNA splicing and trafficking, rRNA synthesis, apoptosis, angiogenesis, and cytokine activities in inflammation (Lee *et al.*, 2004; Park *et al.*, 2005b). Although the pleiotropic activities of these enzymes may give a benefit to cells, they appear to be also pathologically associated with cancer or other diseases (Ivakhno and Kornelyuk, 2004).

Among 20 different ARSs, tryptophanyl-tRNA synthetase (WRS) possesses 11 putative protein kinase motifs and is known as a phosphoprotein but its molecular mechanisms in cellular signaling pathways remain unresolved. In mammalian cells, WRS is activated for angiostatic signaling by proteolysis or alternative splicing to give two natural variants – mini-WRS and T2-WRS (Otani *et al.*, 2002a). Expression of mini-WRS is strongly induced by anti-proliferative cytokine interferon- γ along with other angiostatic factors such as IP-10 (interferon inducible protein 10) and MIG (monokine induced by IFN- γ) (Fleckner *et al.*, 1995; Salvucci *et al.*, 2004; Turpaev *et al.*, 1996). Mini- and T2-WRS inhibit development of new vessels without affecting pre-established vasculature (Otani *et al.*, 2002a; Wakasugi *et al.*, 2002a). The anti-angiogenic activity of both fragments has been demonstrated in cell-based assays *in vitro* and *in vivo* (Otani *et al.*, 2002a; Wakasugi *et al.*, 2002a). These cytokine fragments of WRS inhibit the migration of

*Address correspondence to this author at the National Creative Research Initiatives Center for ARS Network, College of Pharmacy, Seoul National University, San 56-1, Shillim-dong, Kwanak-gu, Seoul 151-742, Korea; Tel: 82-2-880-8180; Fax: 82-2-875-2621; E-mail: sungkim@snu.ac.kr

Table 1. Functions of Translational Components in Protein Synthesis

		Eukaryotic Factors	Functions
ARS Complex		20 ARSs AIMP3/p18 AIMP2/p38 AIMP1/p43	Aminoacylation of respective tRNAs ARS complex stability, DNA repair ARS complex stability, lung differentiation Interacting RRS, inflammatory cytokine, wound healing, angiogenesis control Hormonal activity for glucose homeostasis
Initiation Factors		eIF1 eIF1A eIF2 α,β,γ eIF2A eIF2B $\alpha,\beta,\gamma,\delta,\epsilon$ eIF2C eIF3a,b,c,d,e,f,g,h,i,j,k eIF3A eIF4A Ded1 eIF4B eIF4E eIF4F eIF4G eIF4H eIF5 eIF5A eIF5B	Simulation of Met-tRNAi & mRNA binding to 40 S ribosomes Simulation of Met-tRNAi & mRNA binding to 40 S ribosomes Met-tRNAi binding to 40 S ribosomes AUG-dependent Met-tRNA binding to 40 S ribosomes GDP:GTP exchange on eIF2 Stabilization of ternary complex Ribosome dissociation, Stabilization of ternary complex Stimulation of mRNA binding Ribosome dissociation mRNA binding, RNA helicase mRNA binding, RNA helicase mRNA binding, RNA helicase mRNA binding, Caprecognition mRNA binding, Caprecognition, RNA helicase mRNA binding, Anchorprotein mRNA binding Ribosomal subunit joining Ribosomal subunit joining, Formation of the peptide bond Ribosomal subunit joining
Elongation Factors		eEF1A1 eEF1A2 eEF1B α eEF1B β eEF1B γ EF2	Recruits tRNA to ribosomal A site;GTP hydrolysis Recruits tRNA to ribosomal A site;GTP hydrolysis GDP:GTP exchange on eEF1A GDP:GTP exchange on eEF1A Links eEF1B α and eEF1B β during GDP:GTP exchange Ribosomal translocation on mRNA;GTP hydrolysis
Releasing Factors		eRF1 eRF3	Catalyse peptidyl-tRNA hydrolysis eRF-dependent and ribosome-dependent
Ribosomal Complex	Small subunit	S2,S3,S3a,S4,S5,S6,S7,S8 S9,S11,S12,S13,S15,S16,S17, S19,S20,S23,S24,S25,S26, S27,S28,S30	Link specific amino acids into polypeptide chains according to genetic information transported in ribonucleic acid
	Large subunit	L3,L4,L5,L6,L7,L8,L9,L10,L11, L12,L13,L13a,L17,L18,L18a,L19. L21,L22,L23,L23a,L24,L26,L27, L27a,L28,L29,L30,L32,L35,L35a, L37,L37a,L38,L39,L41,L44, P0,P1,P2,L3(Mito),L31(Mito)	

ECs (Otani *et al.*, 2002a; Wakasugi *et al.*, 2002a), and activation of extracellular signal-regulated kinase (ERK1/2) and Akt (Tzima *et al.*, 2003) and induce apoptosis of human umbilical vein endothelial cells (Otani *et al.*, 2002b; Wakasugi *et al.*, 2002b). Since anti-angiogenic therapy shows great potential to control tumor progression, a new angiogenesis-signaling pathway that is regulated in part by WRS, is of great interest for cancer therapy. Since T2-WRS is the natural fragment of a tRNA synthetase and does not seem to have the anti-angiogenic effect on the normal vasculature, it might be safely used to block neovascularization of tumors (Tzima *et al.*, 2005). In addition, human WRS expression was shown to correlate with growth rates of neuroblastoma and pancreatic cancer cells (Paley *et al.*, 2007). Also, the production of anti-WRS autoantibodies was found in the sera of some donors and cancer patients, indicating a potential relationship to interferon induction (Paley *et al.*, 1995). Furthermore, WRS has been known as a marker protein of monocyte maturation to macrophage and its mRNA expression is significantly upregulated during the maturation of tissue macrophage (Krause *et al.*, 1996). Monocytes not only settle in organs as a physiological process, but also enter tumor tissues, generating a population of macrophages, which are termed as tumor-associated macrophages (TAM). Many tumors show a rich leukocytic infiltration consisting of lymphocytes as well as of TAM (Mantovani *et*

al., 1992). Because macrophages exert a higher degree of tumor cytotoxicity than monocytes (Krause *et al.*, 1996), WRS might have some critical roles in the maturation and function of macrophages in cancer.

KRS is secreted from various cell lines in response to TNF- α (Park *et al.*, 2005c) and stimulates macrophages and peripheral blood mononuclear cells to enhance migration and TNF- α production. Thus, KRS and TNF- α appear to form a positive feedback loop to amplify secretion of both factors. Interestingly, KRS was found to be highly expressed in the tumor regions of the breast cancer patients (Park *et al.*, 2005c; Gene Expression Omnibus database). Although the biological meaning of KRS secretion is not yet understood, it may be linked to the survival or metastasis of cancer cells. In this regard, it is worth noting that the cancer cells can turn TNF- α to a proliferative signal (Young and Wright, 1992) although TNF- α normally suppresses cell proliferation and induces cell death (Baisch, 2002; Ichijo *et al.*, 1997; Liu *et al.*, 2002; Tobiume *et al.*, 2001). Thus, KRS may help the growth of cancer cells directly or indirectly through the induction of TNF- α secretion.

Methionyl-tRNA synthetase (MRS) plays a role in the maintenance of translational fidelity (Deniziak and Barciszewski, 2001).

Human MRS was shown to be translocated to the nucleoli under proliferative conditions to augment rRNA synthesis although the underlying mechanism is not clearly understood (Ko *et al.*, 2000). It was previously demonstrated that the MRS activity is increased in human colon cancer (Kushner *et al.*, 1976). Interestingly, the MRS-encoding gene is overlapped with the CHOP (C/EBP homologous protein) gene in a 56 bp domain corresponding to its 3' end of human chromosome 12q13 (Fig. 1A). It is known that the CHOP expression is associated with several forms of human cancer. Specifically, amplification of this region occurs in several forms of human cancer such as human sarcomas (Forus *et al.*, 1994; Nilbert *et al.*, 1995), malignant fibrous histiocytoma (Palmer *et al.*, 1997), and gliomas and glioblastomas (Reifenberger *et al.*, 1996). A consequence of the overlap between the CHOP and MRS genes causes an amplification of the 12q13 locus in sarcomas (Forus *et al.*, 1994; Nilbert *et al.*, 1995) and other forms of human tumors (Palmer *et al.*, 1997; Reifenberger *et al.*, 1996), probably resulting in overexpression of the MRS and CHOP gene, which may give a growth advantage to some cells that could contribute to tumor progression. In addition, the regulation of MRS expression could be altered in myxoid liposarcoma as a result of the chromosomal translocation and an increased level of MRS could provide liposarcoma cells with a significant growth advantage. Furthermore, amino acid deprivation induces the expression of CHOP (Bruhat *et al.*, 1997; Marten *et al.*, 1994) and regulates the activity of MRS (Lazard *et al.*, 1987). Therefore, there might be an intimate functional interaction between the two genes. Also, the interaction between the overlapping CHOP and MRS mRNAs would have important implications for their regulation in cellular response to environmental stress, and oncogenic transformation in which amplifications or translocations of the CHOP gene occur (Ubeda *et al.*, 1999).

Cysteinyln-tRNA synthetase (CRS) is often detected as a fusion protein with anaplastic lymphoma kinase (ALK) in inflammatory myofibroblastic tumor (IMT) that is a rare childhood neoplasm characterized by a prominent inflammatory infiltrate (Cools *et al.*, 2002; Debelenko *et al.*, 2003). Recently, the recognition of IMT has been considered as a distinctive neoplastic process because of overlapping pathologic and clinical features with reactive (nodular fasciitis, scars, or desmoid fibromatosis) and/or sarcomatous processes. A large subgroup of IMTs shows clonal rearrangements involving chromosomal band 2p23, the site of the *ALK* gene, and molecular analyses have demonstrated the expression of a number of *ALK* fusion genes (*TPM3-ALK*, *TPM4-ALK*, *CLTC-ALK*, *CARS-ALK*) (Bridge *et al.*, 2001; Cook *et al.*, 2001; Cools *et al.*, 2002; Duyster *et al.*, 2001; Griffin *et al.*, 1999; Lawrence *et al.*, 2000; Su *et al.*, 1998; Yousef *et al.*, 2001). Anti-*ALK* immunohistochemical studies showed abnormally upregulated *ALK* expression in 60% (44 of 73) of cancer cases, suggesting that *ALK* fusions would play a crucial role in the pathogenesis of these tumors (Cook *et al.*, 2001). The CRS and *ALK* genes have been mapped to 11p15.5 and 2p23, respectively (Cruzen *et al.*, 1993; Morris *et al.*, 1997). The detection of the CRS-*ALK* fusion in IMT case is characterized by the presence of t(2;11;2)(p23;p15;q31) and chimeric protein of approximately 130 kDa (Fig. 1B). In this chimeric protein, the 606 N-terminal amino acid peptide of CRS is fused to the 562 amino acids of *ALK* (Cools *et al.*, 2002; Debelenko *et al.*, 2003). Chromosome 11p15.5 has been identified as an important region of tumor-suppressor gene, showing LOH in Wilm's tumor, rhabdomyosarcoma, lung, ovarian, and breast cancer (Gicquel *et al.*, 1997; Karnik *et al.*, 1998; Kerr *et al.*, 2003; Xu *et al.*, 2001). The CRS gene is located only 700 kb telomeric to Nup98 that is frequently involved in translocations in acute myeloid leukemia (Hu *et al.*, 1997). Thus, the genes on 11p15.5 containing CRS may be involved in the malignancies including this region.

Phenylalanyl-tRNA synthetase (FRS) is the most complex enzyme among ARSs (Mirande, 1991), consisting of heterodimeric enzyme of the $\alpha_2\beta_2$ type in all species, and it is markedly conserved

during evolution from prokaryotes to eukaryotes (Schimmel, 1987). The crystal structure of FRS from *Thermus thermophilus* consists of 11 structural domains containing three in the α subunit and eight in the β subunit (Mosyak *et al.*, 1995). The gene encoding the α subunit of FRS is mapped to chromosome 19 (Sen *et al.*, 1997). Interestingly, abnormalities in this region have been reported in lung solid tumor (Mittelman, 1991). The α subunit of FRS shows preferential expression in tumorigenic acute-phase chronic myeloid leukemia K562 cells, and the karyotype of the A549 cell line also shows trisomy of chromosome 19 along with other chromosomal translocations (Lieber *et al.*, 1976). This is the first case of tumor-selective, cell cycle-dependent and differentiation-dependent expression among ARSs (Sen *et al.*, 1997). While the α -subunit domains of FRS create catalytic module and a coiled-coil domain directly involved in aminoacylation and tRNA-Phe binding, the β -subunit is a collection of structural domains that are likely to perform various functions (Rodova *et al.*, 1999).

The glycyl-tRNA synthetase (GRS)-encoding gene is localized on chromosome 7p15 region (Nichols *et al.*, 1995), and was recently identified as a potent tumor-promoting gene through microarray analysis (Wasenius *et al.*, 2003). This gene is overexpressed > 2 fold in papillary thyroid carcinoma (PTC) (Table 2), which is the most common type of the thyroid cancer and frequently gives rise to cervical lymph node metastasis (Schlumberger, 1998). The research based on comparative genomic hybridization (CGH) suggested that the copy number of this gene changes at 12-48% in PTC (Kjellman *et al.*, 2001). The DNA amplification in PTC has been found in 1q23-ter, 2, 7p, 11p15-ter, 14q, 19q, and X regions (Hemmer *et al.*, 1999; Kjellman *et al.*, 2001). Although GRS was also identified as a novel candidate gene implicated in hypoxia signal transduction pathway in human hepatocellular carcinoma cells (Scandurro *et al.*, 2001), its role at molecular level awaits further investigation.

Instability at microsatellite regions (MSI) is one of the characteristics of tumors from patients having germline mutations of DNA mismatch repair genes. Through mutation analysis of the repeated sequences in the coding and 5' upstream regions of MSI-high colorectal tumors that are from the patients having hereditary nonpolyposis colorectal cancer (HNPCC) and Turcot syndrome, alteration was found at the (A)₁₀(TA)₉ in the 5' upstream region of human mitochondrial isoleucyl-tRNA synthetase (IRS) in 59% of tumors, but not in the repeated sequences of cytoplasmic IRS (Miyaki *et al.*, 2001). With these findings, mutation of the 5' upstream regions seems to be implicated in mitochondrial malfunctions in HNPCC and Turcot syndrome (Miyaki *et al.*, 2001). IRS as well as glutamyl-prolyl bifunctional tRNA synthetase (EPRS) (Menssen and Hermeking, 2002) that makes interaction with IRS (Rho *et al.*, 1996), are the target genes of c-Myc protooncogene (Fig. 3) (Coller *et al.*, 2000).

AMINOACYL-tRNA SYNTHETASE-INTERACTING MULTIFUNCTIONAL PROTEINS

Several mammalian ARSs are capable of forming various protein complexes. Among them, a macromolecular complex consisting of nine different ARSs is the most intriguing (Ko *et al.*, 2002; Lee *et al.*, 2004; Park *et al.*, 2005b). This complex also harbors three non-enzymatic factors designated AIMP (aminoacyl-tRNA synthetase-interacting multi-functional proteins). They are AIMP1, 2 and 3 that were previously named as p43, p38 and p18, respectively. Although they play scaffolding roles in the assembly of the whole complex (Han *et al.*, 2006; Kim *et al.*, 2002), they are also involved in numerous other biological processes. In the multi-ARS complex, AIMP1 associates with arginyl-tRNA synthetase (RRS), facilitating its catalytic activity (Kim *et al.*, 2000). Interestingly, AIMP1 is also secreted from different cells such as prostate cancer (Barnett, 2000) and pituitary adenomas (Bottoni *et al.*, 2005). The impaired secretion of AIMP1 in combination with the sporadic

Table 2. Cancer-Dependent Overexpression of ARSs

ARSs	Related Tumor	References
GRS	Hepatocellular carcinoma cells Papillary thyroid carcinoma cells	Scandurro <i>et al.</i> , 2001 Wasenius <i>et al.</i> , 2003
MRS	Human colon cancer Sarcomas Malignant fibrous histiocytomas Malignant gliomas and glioblastomas	Kushner <i>et al.</i> , 1976 Forus <i>et al.</i> , 1994 Nilbert <i>et al.</i> , 1995; Palmer <i>et al.</i> , 1997 Reifenberger <i>et al.</i> , 1996
FRS	A subunit; preferential expression in tumorigenic human Acute-phase chronic myeloid leukemia K562 cells A-subunit mRNA : overexpressed in the same acute-phase chronic myeloid leukemia cells line Undifferentiated promyelocytic leukemia cells Chronic myeloid leukemia cells Lymphoblastic leukemia cells Burkitt's lymphoma Colorectal adenocarcinoma cells Lung carcinoma cells Melanoma cells	Lieber <i>et al.</i> , 1976 Rodova <i>et al.</i> , 1999 Rodova <i>et al.</i> , 1999
RRS	Pituitary adenoma	Bottoni <i>et al.</i> , 2005
CRS	Inflammatory myofibroblastic tumor	Cools <i>et al.</i> , 2002; Debelenko <i>et al.</i> , 2003
WRS	Neuroblastoma and pancreatic cancer dells	Paley <i>et al.</i> , 2007
AIMP1	Prostate cancer Pituitary adenomas Hela and MCF 7 cell lines	Barnett <i>et al.</i> , 2000 Barnett <i>et al.</i> , 2000 Barnett <i>et al.</i> , 2000
Emapll	LNCAp and DU-145 prostate adenocarcinoma cells	Barnett <i>et al.</i> , 2000
IRS	Aletration at the (A) 10 (TA) 9 in 5' upstream regions of human mitochondrial isoleucyl-tRNA synthetase(IRS) in 59% of tumors	Miyaki <i>et al.</i> , 2001
KRS	Breast cancer	Park <i>et al.</i> , 2005c

expression of TNF- α could contribute to the progress and growth of pituitary tumors (Schwarz *et al.*, 1999). The secreted AIMP1 controls angiogenesis (Park *et al.*, 2002) and systemic administration of the purified AIMP1 suppressed cancer progression (Lee *et al.*, 2006), implying its potential as anti-cancer therapeutic agent. The AIMP1 secretion inversely correlates with RRS expression and tumor diameter, which in turn negatively correlates with Micro-RNA16-1 (miR16-1) expression in pituitary adenomas, meaning that overexpression of RRS may hold AIMP1 within the multi-ARS complex, preventing AIMP1 secretion (Bottoni *et al.*, 2005). Coincidentally, miR16-1 gene which is located at chromosome 13q14 is deleted in many pituitary adenomas (Fan *et al.*, 2001).

AIMP2 (previously designated p38 or JTV-1), is also associated with the multi-ARS complex, playing a scaffold role in the assembly of the components (Han *et al.*, 2006; Lee *et al.*, 2004). AIMP2 was demonstrated to downregulate c-Myc expression through the inhibitory interaction with FUSE-binding protein (FBP), a transcriptional activator of c-Myc (Kim *et al.*, 2003). The binding of AIMP2 to FBP stimulates ubiquitination and degradation of FBP, leading to downregulation of c-Myc, which is required for the differentiation of functional alveolar type II cells. Thus, AIMP2-knockout mice caused neonatal lethality due to the respiratory distress syndrome resulting from hyperplasia of lung epithelial cells. AIMP2 is also translocated into nucleus by transforming growth factor- β (TGF- β). This work identified a new activity of AIMP2 as a mediator of TGF- β signaling and its functional importance for lung cell differentiation (Kim *et al.*, 2003). c-Myc is one of the well-known proto-oncogenes (Castresana *et al.*, 1992) and TGF- β signaling pathway is crippled in different types of cancers (Markowitz and Roberts, 1996). If AIMP2 mediates TGF- β signaling to c-Myc, its inactivating mutations or abnormal expression may be associated with cancer formation. The gene encoding AIMP2 is positioned complementary to PMS2 that is known to be

an oncogene (Francia *et al.*, 2004; Nicolaidis *et al.*, 1995) (Fig. 1C). It would be interesting to see whether the two proteins give an influence to the expression of their counterparts.

The smallest factor, AIMP3/p18 is bound to the multi-ARS complex through the specific interaction with MRS (Lee *et al.*, 2004). Although biological function for the interaction of AIMP3 with MRS within the complex has not been understood, its role was unveiled in the maintenance of chromosomal DNA (Park *et al.*, 2005b). AIMP3 is translocated into nucleus upon DNA damage to upregulate p53 by direct activation of ATM/ATR. While AIMP3 knock-out results in early embryonic lethality, the heterozygous mice become highly susceptible to spontaneous tumor formation at various tissues (Park *et al.*, 2005a), and AIMP3 haploid cells also showed reduced chromosome stability, and abnormal cellular and nuclear division (Park *et al.*, 2006), demonstrating its significance as haploinsufficient tumor suppressor. Thus, all of these three ARS-interacting factors appear to be functionally linked to control cancer formation with their unique mechanisms.

TRANSLATION INITIATION FACTORS

Translational initiation is a central control site in protein synthesis including at least 25 different factors. Modulations of the initiation machinery including phosphorylation of initiation factors and their controlled association with other proteins can regulate both specific mRNAs and overall translation rates to affect cell growth and phenotypes (Gray and Wickens, 1998). Accumulating evidences show that eIFs may be important in the regulation of cell growth or survival in addition to translational initiation, particularly for the case of eIF2, eIF4E, eIF4G and eIF5. Also, the expression of eIFs is abnormally elevated in diverse cancers implicating their involvement in cell transformation (Fig. 2). eIF4E has been a focus as a representative multifunctional regulatory protein that control gene expression in both nucleus and cytoplasm (Wilkinson and Shyu, 2001). The involvement of eIF4E in tumorigenesis has been

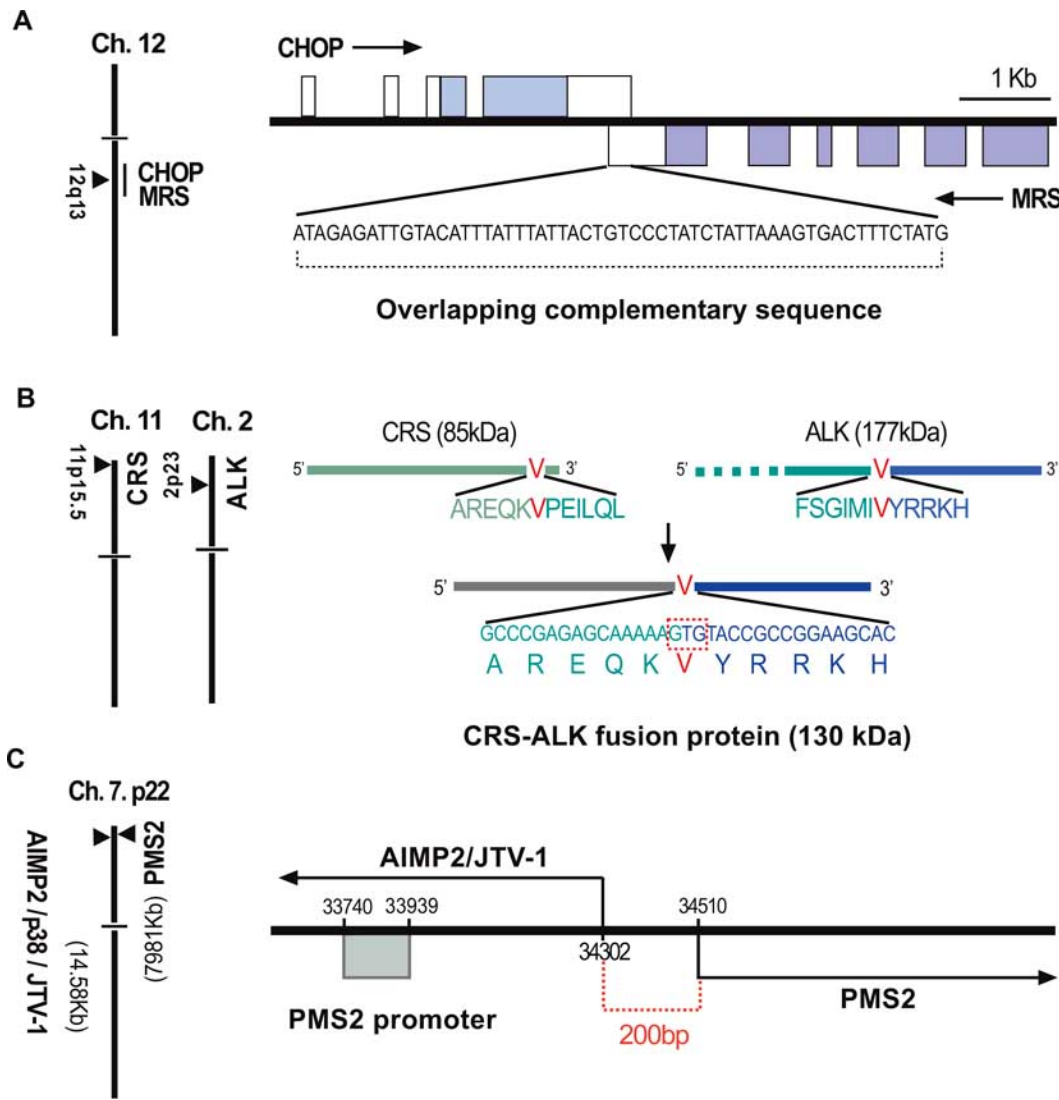


Fig. (1). Schematic representation of genomic arrangement of ARSs and AIMP2. (A) MRS (methionyl-tRNA synthetase) and CHOP (C/EBP homologous protein) genes reside on chromosome 12q13 and share a sequence of 39 bases in their respective ends. (B) The chromosomal loci of CRS (cysteinyl-tRNA synthetase) and ALK (anaplastic lymphoma kinase) (left) and their fusion sites (right) are shown. Note the last base of the CRS portion of the sequence (G) contributes to the GTG triplet encoding valine (red), maintaining the in-frame translation of the ALK catalytic domain at the C terminus of the predicted chimeric protein. (C) The chromosomal loci of AIMP2/p38/JTV-1 and PMS2 are shown (left). The human AIMP2/p38/JTV-1 and PMS2 genes are located in opposite orientation with approximately 200 bp distance between their transcription start sites.

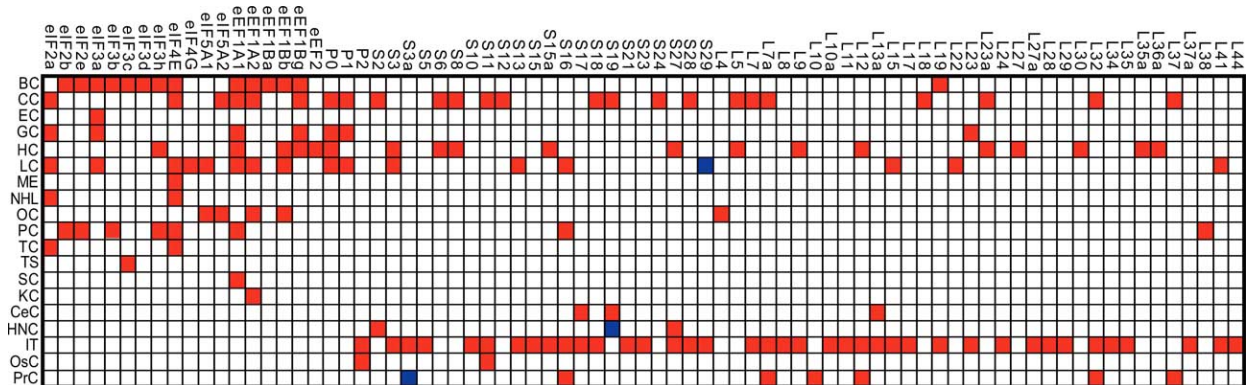


Fig. (2). Expression profile of translation initiation factors (eIFs), elongation factors (eEFs) and ribosomal proteins (RPs) in various human cancers. Translational components are overexpressed (red) or downregulated (blue) in a wide range of cancers. BC: breast cancer, CC: colon cancer, EC: esophageal cancer, GC: gastric carcinoma, HC: hepatocellular carcinoma, LC: lung cancer, ME: melanoma, NHL: non-Hodgkin's lymphoma, OC: ovarian cancer, PC: pancreatic cancer, TC: thyroid carcinoma, TS : testicular seminomas, SC: stomach cancer, KC: kidney cancer, CeC: cervical cancer, HNC: head and neck squamous cancer, IT: intracranial teratoma, OsC: osteosarcoma, PrC: prostate cancer.

shown over the past decade, and its overexpression results in dramatic phenotypic changes such as rapid cell proliferation, loss of contact inhibition, growth in soft agar and tumor formation in nude mice (Clemens, 2004; De Benedetti and Harris, 1999). It also facilitates the synthesis of two powerful tumor angiogenic factors (VEGF and FGF-2) by selectively enhancing their translation, and correlation with these angiogenic factors potentiates its possible role in angiogenesis (De Benedetti and Harris, 1999). These results were confirmed by *in vivo* experiments, which showed the significant increase of eIF4E in breast invasive ductal carcinomas and the islets of viable cells in the center of poorly vascularized ductal carcinomas. Also, eIF4E expression is increased in early confined breast cancer lesions by hypoxia (DeFatta *et al.*, 1999). On the contrary, the cells with reduced eIF4E expression showed delayed, reduced invasiveness and decreased experimental metastasis in Ras-transformed clone of rat embryo fibroblasts (Graff *et al.*, 1995).

Increased level of eIF4E might have influence on the expression level of some mRNA such as the Src family member, c-Myc, cyclinD1, VEGF, and FGF-2, which have critical roles in the regulation of cell growth or survival (Clemens, 2004; De Benedetti and Harris, 1999). In addition, gene amplification of eIF4E was also observed in the majority of human non-small-cell lung cancers, some breast cancer, and some benign and malignant tumors of head and neck (Thornton *et al.*, 2003). The human gene encoding eIF4E is mapped to chromosome 4q21-22, and frequently amplified in prostate cancer of African Americans (Cher *et al.*, 1996). Thus, the cancer-associated overexpression of eIF4E could be explained by the amplification of the encoding gene. With all of these results, eIF4E is the first human oncogene among the components of the protein translation machinery that has a critical role in various human cancers (Clemens, 2004; Thornton *et al.*, 2003).

Overexpression of eIF4G may be also related to oncogenic transformation and its expression is also increased in the squamous cell lung carcinomas with gene amplification (Clemens, 2004). The human gene encoding eIF4G is mapped to chromosome 3q27-qter (Yan and Rhoads, 1995), and amplified within 3q26-q27 in squamous cell lung carcinomas (Keiper *et al.*, 1999). Also, it is the putative target gene induced by c-Myc (Coller *et al.*, 2000) (Fig. 3). The transcript of eIF4G2 gene is downregulated in the transitional cells of bladder carcinoma, and this downregulation is significantly associated with invasive tumors (Buim *et al.*, 2005). This gene is mapped to chromosome 11p15.3 (Imataka *et al.*, 1997). Because deletion of chromosome 11 is observed in invasive bladder tumors, this region might harbor important tumor suppressor genes (Henis-Korenblit *et al.*, 2002; Zhang *et al.*, 2004).

eIF4A is an ATP-dependent RNA helicase, allowing the 40S ribosomal subunit to bind RNA and to search for the initiation site. In mammals, three isoforms of eIF4A have been identified. Among these, eIF4A1 has been considered as a putative proto-oncogene (Eberle *et al.*, 1997). It is induced by n-Myc (Boon *et al.*, 2001) (Fig. 3), and differentially expressed in human melanoma cells and normal melanocytes (Fig. 2). Particularly, only eIF4A1 mRNA is consistently overexpressed in malignant melanomas (Kraehn *et al.*, 1995). Antisense RNA against eIF4A1 mRNA decreased proliferation of human melanoma cell lines although its overexpression was not sufficient for transformation of other cell lines (Eberle *et al.*, 2002).

eIF5A is phylogenetically conserved from yeast to mammalian cells (Caraglia *et al.*, 2000). Although the precise function of eIF5A in translation initiation is not known yet, the accumulated evidences suggested that it is a multifunctional protein regulated through diverse mechanisms. Its potential functions include nucleocytoplasmic shuttle for specific subsets of mRNA, mRNA stability, transport of HIV mRNA (Hofmann *et al.*, 2001), cell proliferation and apoptosis (Jakus *et al.*, 1993; Kang and Hershey, 1994; Park *et al.*, 1998; Shi *et al.*, 1996; Wang *et al.*, 2001). It is the only cellular protein known to contain the unique spermidine-derived amino acid

hypusine (at Lys50 in human eIF5A) that appears to be required for cell proliferation. Previous studies showed that mutation (Lys50Arg) or intracellular depletion of eIF5A gene inhibits cellular proliferation (Caraglia *et al.*, 2000) and the inhibition of deoxyhypusine synthase impedes the growth of several cell lines, including malignant human cell. Hypusine-containing eIF5A promotes the association of a subset of proliferation-related mRNAs with polysomes facilitating translation, and with putative motifs of hypusine-dependent mRNAs which are located in the UTRs of cyclin D1 (Hanuske-Abel *et al.*, 2002) or cyclooxygenase-2 mRNA (Parker and Gerner, 2002) that are essential in cell cycle and cancer, respectively.

eIF5A exists as two or more isoforms in many eukaryotic organisms (Jenkins *et al.*, 2001). In human, the two isoforms, eIF5A1 and eIF5A2, share 84% of amino acid identity, but their encoding genes are mapped to chromosomes 17p12-13 (Steinkasserer *et al.*, 1995) and 3q26.2 (Guan *et al.*, 2001), respectively. Recent studies suggested that both isoforms are implicated in certain types of human cancers. eIF5A1 is highly expressed in lung and some ovarian cancers (Chatterjee *et al.*, 2006; Chen *et al.*, 2003) (Fig. 2) and responsive to c- or n-Myc stimulation (Boon *et al.*, 2001; Coller *et al.*, 2000; Menssen and Hermeking, 2002) (Fig. 3). The eIF5A2 expression is also enhanced in testis and colon cancers (Guan *et al.*, 2001; Jenkins *et al.*, 2001) (Fig. 2). Especially, amplification of 3q26 is one of the most frequent chromosomal alterations in various solid tumors containing ovarian cancer, suggesting the presence of one or more oncogenes in this region (Forozan *et al.*, 2000). Interestingly, the eIF5A2 gene has been isolated from a frequently amplified region at 3q26.2 using chromosome microdissection-hybrid selection method (Guan *et al.*, 2001), and its tumorigenic ability was confirmed by anchorage-independent growth in soft agar and tumor formation in nude mice as well as using antisense DNA of eIF5A2 in ovarian cancer cell line (Guan *et al.*, 2004). eIF5A2 plays an important role in eukaryotic cell survival (Clement *et al.*, 2003), and its overexpression is associated with the advanced stage of ovarian cancer (Guan *et al.*, 2004). All of these results suggest that eIF5A1 and eIF2 might play an important role as putative oncogene in ovarian cancer.

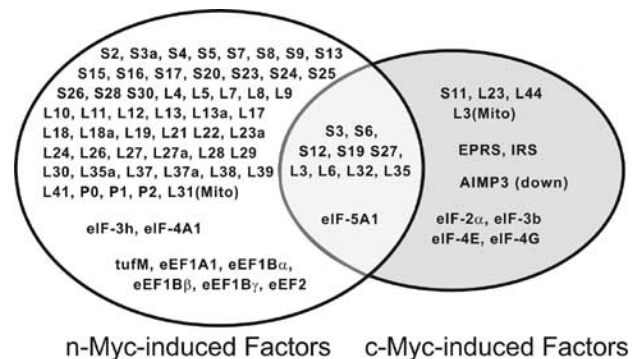


Fig. (3). Myc regulates the expression of proteins involved in translation. Many translational factors are upregulated in Myc-overexpressing cells. S3, S6, S12, S19, S27, L3, L6, L32, L35 and eIF5A1 are increased by both of c-Myc and n-Myc.

Deregulation of eIF2 α might be related to tumorigenesis. Phosphorylation of eIF2 α through activation of eIF2 α kinase such as PKR and HCR decreases the initiation of translation. The enforced expression of either nonphosphorylatable eIF2 α (S51A mutant) or dominant negative PKR mutant cause malignant transformation of NIH3T3 cells and the development of tumors in nude mice (Clemens, 2004). The elevated expression of eIF2 α has been also

shown in the diverse cancers (Fig. 2). Highly expressed eIF2 α is redistributed towards nucleus in gastrointestinal carcinomas and it is also highly expressed in c-Myc, v-Src, and v-abl-transformed cells, together with eIF4E (Rosenwald, 1996).

Eukaryotic initiation factor eIF3 contains at least thirteen non-identical subunits, named from eIF3a to eIF3m with an apparent mass of approximately 700 kDa, and plays an essential role in the rate-limiting initiation phase of translation (Mayeur *et al.*, 2003; Zhang *et al.*, 2007). Aberrant mRNA and protein levels of several eIF3 subunits have been detected in a wide variety of solid tumors and cancer cell lines. Especially, increased mRNA and protein levels of the eIF3a, b, c, h and i subunits have been detected in a wide variety of human tumors, and frequently identified as prognostic biomarkers for poor clinical outcome, suggesting that these initiation factors may be promising therapeutic targets for treating cancer. The decreased expression of eIF3a in human lung cancer cell line and breast cancer cell line significantly reversed their malignant growth phenotype (Dong *et al.*, 2004), and different isoforms of eIF3a are overexpressed in mouse melanoma and Hela cells, human breast, cervical, esophageal, lung and gastric cancers (Zhang *et al.*, 2007). eIF3c is overexpressed in testicular seminomas and breast adenocarcinoma cells (Joseph *et al.*, 2004; Rothe *et al.*, 2000). Although its function and mechanism in tumorigenesis are unclear, some studies suggested that loss of chromosome 16p region containing the eIF3c gene correlates with seminomas (Summersgill *et al.*, 1998). eIF3e is important in the regulation of cell proliferation and highly conserved subunit through evolution (Burks *et al.*, 2001). It is encoded by the *Int6* gene, a common integration site of mouse mammary tumor virus leading to the production of a truncated eIF3e (Miyazaki *et al.*, 1997). In contrast with the full-length eIF3e, overexpression of truncated eIF3e causes the malignant transformation on mammary epithelial cells and NIH3T3 cells, and injection of these cells leads to tumor development in nude mice (Mayeur and Hershey, 2002). However, another study showed that eIF3e expression was reduced in primary human breast and non-small cell lung carcinomas (NSCLC), which frequently exhibits LOH at the eIF3e locus (Buttitta *et al.*, 2005). Since many portions among NSCLC tumor samples were hypermethylated in the transcription promoter and first exon region, eIF3e expression might represent new prognostic marker in the patients with stage I of NSCLC (Buttitta *et al.*, 2005). Interestingly, subcellular localization of eIF3e is cell-cycle dependent, being maximal in nucleus of early S phase, and different between primary human fibroblasts and transformed counterparts. Therefore, deregulation in subcellular localization of eIF3e may be a feature of malignant human cells (Watkins and Norbury, 2004). eIF3h is overexpressed in breast and prostate cancer (Caraglia *et al.*, 2000). Many studies with CGH showed that the most common chromosomal aberrations are the loss of 1p, 6q, 8p, 10q, 13q, 16q and 18q, and gain of 1q, 2p, 7, 8q, 18q and Xq in prostate cancer (Visakorpi, 2003). Particularly, the gain of 8q was also a common genetic alteration in breast and prostate cancers (Isola *et al.*, 1995; Sato *et al.*, 1999). CGH analysis confirmed that there are at least two independently amplified subregions, 8q21 and 8q23-q24, suggesting the presence of several amplified target genes (Nupponen *et al.*, 1998), including the well-known c-Myc oncogene at 8q24.1. However, eIF3h amplification is not always associated with c-Myc amplification in breast and hepatocellular carcinoma (Okamoto *et al.*, 2003). Using the suppression subtractive hybridization analysis, eIF3h was identified to be overexpressed in breast cancer cell line as well as prostate and breast tumors (Joseph *et al.*, 2004; Nupponen *et al.*, 1998) (Fig. 2). Based on these studies, eIF3h appears to be the strongest target gene in the gain of 8q (Savinainen *et al.*, 2004). Particularly, eIF3h may be also involved in progression of prostate and hepatocellular carcinomas (Okamoto *et al.*, 2003; Saramaki *et al.*, 2001). Since eIF3h was identified as a target gene of n-Myc (Boon *et al.*, 2001) (Fig. 3), genomic aberrations of eIF3h might contribute to the pathogenesis of breast, prostate and hepatocellular carcinomas. Human eIF3i

showed 99% similarity to the predicted protein of mouse TIF3 cDNA (GeneBank accession number AF271072) which was identified as a novel cadmium chloride (CdCl₂)-responsive proto-oncogene (Joseph *et al.*, 2002). Its oncogenic potential was confirmed by several *in vitro* experiments and tumor formation in nude mice. Expression of antisense RNA against TIF3 mRNA resulted in the reversal of oncogenic potential of the CdCl₂-transformed BALB/c-3T3 cells, suggesting its therapeutic potential especially to CdCl₂-induced cancer cells (Joseph *et al.*, 2004).

ELONGATION FACTORS

The elongation phase of translation consists of two kinds of eukaryotic elongation factors (eEFs), eEF1A and B, to recruit the aminoacyl-tRNAs to the A-site of the ribosome, and eEF2 to mediate the translocation step of ribosome (Galasinski and Moldave, 1969; Kaziro *et al.*, 1991; Moldave, 1985; Taira *et al.*, 1972). eEFs are also implicated in various cellular processes or diseases involving translational control, signal transduction, cytoskeletal organization, apoptosis, autoimmune disease, oncogenic transformation, nutrition, and nuclear processes such as RNA synthesis and mitosis (Ejiri, 2002). Furthermore, some eEFs including eEF1A1, eEF1B α , eEF1B β , eEF1B γ , eEF2 and the mitochondrial elongation factor Tu are the target genes for n-Myc (Boon *et al.*, 2001) (Fig. 3).

eEF1 consists of four different subunits (1A, 1B α , 1B β and 1B γ) in mammals (Thornton *et al.*, 2003). Among them, eEF1A exists as two different isoforms (eEF1A1 and eEF1A2) that are expressed in tissue-specific manner. eEF1A1 and A2 share more than 90% of DNA and protein sequences, and have the same enzymatic function. While eEF1A1 is widely expressed, eEF1A2 expression is restricted to brain, heart, and skeletal muscle for unknown reason (Thornton *et al.*, 2003).

eEF1A1 enhances the rate of both spontaneous and chemically induced transformation of mouse and hamster fibroblasts and altered expression of eEF1A1 has been suggested to be linked to transformation phenotypes through several independent studies (Gopalkrishnan *et al.*, 1999; Lamberti *et al.*, 2004). The expression of eEF1A1 was elevated in the breast, colon, lung, pancreas, and stomach tumors (Fig. 2). Overexpression of eEF1A1 was also observed in human head and neck carcinoma cell lines and bronchial epithelial cells transformed with benzopyrene diolepoxide (Johnsson *et al.*, 2000). Furthermore, overexpression of eEF1A1 seems to be correlated with the increased metastatic potential in rat mammary adenocarcinoma through its interaction with actin. Following the stimulation with epidermal growth factor, there is a parallel increase in the amount of F-actin and eEF1A1 associated with cytoskeleton. It has been suggested that a loose association of eEF1A with actin may be related to the metastatic process *via* an altered organization of the actin cytoskeleton and the differential translation of mRNAs associated with cytoskeleton. Since eEF1A1 associates with cellular structures including cytoskeleton and mitotic apparatus, its noncanonical activity is also thought to be closely related to apoptosis and carcinogenesis (Ejiri, 2002). Furthermore, differential RNA display experiment identified that prostate tumor-inducing gene 1 (PTI-1) contains eEF-1A1 sequence with truncated N-terminal residues to amino acid 68 and six additional point mutations (Gopalkrishnan *et al.*, 1999). Since PTI-1 has been proposed as new class of oncogene, this finding adds another evidence to the implication of eEF1A1 for cell transformation.

The human eEF1A2 gene is mapped to 20q13.3, and this region frequently exhibits the amplification in breast, colorectal and ovarian tumors. The amplification of this region in breast and ovarian tumors are associated with poor clinical prognosis and increased tumor aggressiveness. Recently, several studies have suggested that eEF1A2 is a potential oncogene having many oncogenic properties such as the enhancement of foci formation, anchorage-independent growth and the decreases of the doubling time of rodent fibroblasts. Also, eEF1A2 is frequently overexpressed in ovarian tumors, but

not detectable in normal ovary (Abbott and Proud, 2004; Thornton *et al.*, 2003) (Fig. 2). Overexpression of eEF1A2 is also exhibited in 20-35% of human cancer tissues originating from colon, lung, rectum, ovary and kidney (Joseph *et al.*, 2004), while eEF1A1 expression level was unchanged. Interestingly, ectopic expression of eEF1A2 caused transformation of mouse and rodent fibroblasts, and allowed them to grow as tumors when xenografted into mice. Recent analysis of expression profile in 10 different human cancer cell lines revealed that eEF1A2 mRNA is overexpressed in nine cancer cell lines except for malignant melanoma cells. Particularly, its expression was increased as high as approximately 2000-fold in the lung adenocarcinoma cells. Nonetheless, its molecular mechanism in oncogenesis is not fully understood.

eEF1B β (eEF-1 δ) is overexpressed in CdCl₂-transformed BALB/c3T3 cells and ectopic expression of eEF1B β protein seems to be also related to oncogenic transformation (Thornton *et al.*, 2003). In addition, overexpression of eEF1B β has been observed in diverse cancers (Fig. 2). In case of oesophageal carcinoma, overexpression of eEF1B β might be related to lymph node metastasis, advanced disease stages and poorer prognosis for patients (Thornton *et al.*, 2003). Interestingly, its expression pattern exhibits reverse correlation with that of the TSG 14-3-3 sigma in NSCLC, implying the altered expression of both proteins might be involved in lung carcinogenesis (Liu *et al.*, 2004). The cDNA encoding the part of the C-terminal domain of human eEF1B β has been isolated from mammalian cancer cells by subtractive hybridization (Caraglia *et al.*, 2000). eEF1B γ (eEF-1 γ) and eEF1B α (eEF-1 β) are also known to be related to cancers with more circumstantial evidences (Thornton *et al.*, 2003) and their overexpressions have been also observed in diverse cancers (Fig. 2). Like eEF1 components, eEF2 also exhibits the enhanced expression in hepatocellular carcinoma (Caraglia *et al.*, 2000) (Fig. 2).

RELEASING (TERMINATION) FACTORS

In eukaryotic cells, this process requires two classes of eukaryotic Releasing Factors (eRFs), eRF1 and eRF3 (Caraglia *et al.*, 2000; Nakamura *et al.*, 1996). The three types of termination codons are directly recognized by eRF1 to release a synthesized polypeptide chain from ribosome. Recent evidences suggest the potential association of eRFs with the development or progression of cancer although the responsible mechanisms await further investigation.

The eRF1 gene is mapped to 5q31 that contains unidentified genes responsible for genetic or malignant disorders (Guenet *et al.*, 2000). Interstitial deletion of the long arm of chromosome 5q causes recurrent abnormality, mainly concerned with myelodysplastic syndrome and acute myeloid leukemia (AML) (Boulwood *et al.*, 1994). From the aspect of its role in translation termination, deficiency of eRF1 could cause the poor recognition of stop codons, resulting in the read-through with the production of potentially oncogenic aberrant proteins. The eRF1 gene may be myeloid TSG based on the analyses of the human AML cell line HL60, and of the patients suffering from malignant myeloid diseases with cytogenetically defined abnormalities of chromosome 5 (Dubourg *et al.*, 2002).

eRF3 is a GTP-binding releasing factor containing guanine nucleotide binding motifs and has significant sequence homology to the prokaryotic EF-G and EF-Tu. It is a multi-functional protein involved in cell cycle regulation, mRNA decay, cytoskeleton organization, recycle of ribosomes and apoptosis (Hoshino *et al.*, 1999). Like eIFs and eEFs, eRF3 was described to associate with cancer. Overexpression of eRF3 in interstitial type gastric tumors is likely to be involved in tumorigenesis through dysregulating cell cycle, apoptosis, or transcription (Malta-Vacas *et al.*, 2005). The 12 glycine allele was exclusively detected in cancer patients, who have a 20-fold increased risk for gastric cancer, suggesting polyglycine expansion may have a potential role in regulating eRF3 expression

and/or changing the protein function that can lead to gastric cancer development (Brito *et al.*, 2005). Such several trinucleotide repeats have been associated with oncological pathologies, for example androgen receptor gene polymorphisms (Tran *et al.*, 2004).

RIBOSOMAL PROTEINS

The eukaryotic ribosome is composed of four rRNAs and about 80 different ribosomal proteins (RPs) (Woese, 1998; Wool, 1996), while *E. coli* ribosome contains about 54 different RPs (Nakao, *et al.*, 2004). Interestingly, many RPs are involved in extraribosomal functions such as DNA damage repair, replication, transcription, RNA processing, cell growth, apoptosis, transformation and inflammation (Wool *et al.*, 1990; Wool, 1996). Changes in gene expression of specific RPs have been reported in several pathologies including various cancers, abnormal blood cell differentiation, Turner syndrome and Diamond-Blackfan anemia (Ruggero and Pandolfi, 2003). Overexpression of several RPs is shown in diverse cancers (Fig. 2) through the de-regulation at transcriptional (Mager, 1988) or translational level (Kasai *et al.*, 2003). Recently, several hundred lines of zebra fish, each heterozygous for a recessive embryonic lethal mutation, were generated to identify the genes involved in tumorigenesis (Amsterdam *et al.*, 2004). From the analysis, the heterozygous mutations in 11 different RP genes containing S7, S8, S15a, S18, S29, L7, L13, L23a, L35, L36 and L36a predisposed zebra fish to cancer. Since the wild-type allele appeared to be present and did not contain point mutations in the tumors, these results strongly suggest that these 11 genes should be considered as haploinsufficient tumor suppressor genes.

S3a plays an important role in cell transformation and death (Naora, 1999) and is highly expressed in tumor cell lines and tumor tissues. Although ectopic expression of S3a caused transformation of the NIH3T3 cells, it only occurred when S3a overexpressing cells were in close contact, implying that S3a might be involved in cell transformation, but not function as an oncogene. This notion has been supported by the studies that ectopic expression of *fte-1*, the rat homolog of human S3a, failed to induce cell transformation in normal Rat-1 fibroblast cells, but restored the transformed phenotype in revertant *v-fos*-transformed Rat-1 fibroblasts cells in which endogenous *fte-1* was disrupted. Thus, the ability of enhanced S3a expression to induce transformation apparently requires the cooperative effect of the additional signals. Although the molecular mechanism of S3a still remains to be elucidated, it may facilitate an upregulation of oncoproteins or have an extraribosomal function related to cell transformation.

There are substantial evidences suggesting the implications of other RPs in both promoting or inhibiting oncogenic transformation and tumor development. The *Drosophila* homologue of human S29 significantly enhances tumor suppressor of *Krev-1* protein on *v-K-Ras*-transformed fibroblasts, contrasting to those of *fte-1* (Naora, 1999). Recent study suggested that S29 induces apoptosis in NSCLC and augments the effect of anticancer. S6 is implicated in control of cell growth and proliferation. Mutations in *Drosophila* homologue of human S6 caused melanonic tumors formation, lymph gland hyperplasia, and abnormal blood cell differentiation in hematopoietic system, implying its potential tumor suppressive activity (Ruggero and Pandolfi, 2003).

Wilm's tumor is a pediatric nephroblastoma that is derived from embryonal kidney stem cells, and associated with genetic alterations in the 11p13 and 11p15 regions (Beckwith, 1983). Through subtractive cDNA/RNA hybridization between the tumorigenic parent and a nontumorigenic microcell hybrid containing the der (11) chromosome, the putative Wilm's TSG was isolated and designated as QM. The QM-encoded L10 is the mammalian homolog of chicken jun-binding protein (Jif-1), which is a negative regulator of Jun (Chan *et al.*, 1996). QM interacts with proto-oncogene *c-Yes*, and these two proteins are colocalized in several tumor cell lines (Oh *et al.*, 2002). By protein-protein interaction,

QM blocks the c-Yes kinase activity by inhibiting its autophosphorylation, thereby suppressing malignant transformation.

L5, L11 and L23 are associated with oncoprotein MDM2 to form quadruple complex, which stabilizes and activates p53 by inhibiting HDM2-mediated p53 suppression (Dai *et al.*, 2004). Ectopic expression of L5, L11, and L23 reduced HDM2-induced p53 ubiquitination, and induced p53-dependent G1 cell cycle arrest. These results suggest the possibility that some RPs is another regulator of the p53-HDM2 feedback regulation. LOH of L14 has been observed in esophageal squamous cell carcinomas, lung cancer, and squamous cell carcinomas of head and neck (Huang *et al.*, 2006). The L14 gene is mapped to chromosome 3p21.3 region, and L14 protein contains a basic region-leucine zipper-like domain and polymorphic GCT repeats coding polyalanine tract. Allelic loss of chromosome 3p has been observed in multiple malignancies containing carcinoma of breast, female genital tract, kidney, lung, oral cavity, testis, and squamous cell carcinomas of head and neck and esophagus. Tumorigenicity of these carcinoma cell lines was suppressed by the introduction of chromosome 3p and 3p21 fragments (Uzawa *et al.*, 1995). Several TSGs such as *FHIT*, *RASSF1A*, *RAR- β* and *VHL* have been identified in these regions (Kuroki *et al.*, 2003). Recently, alterations of the L14 gene at DNA and RNA levels were observed in esophageal squamous cell carcinomas (Huang *et al.*, 2006).

Ectopic expression of mitochondrial L41 (MRPL41) inhibited the growth of tumor cells (Yoo *et al.*, 2005) and MRPL41 expression was reduced in most tumor tissues. The tumor suppressor effect of MRPL41 might be expressed in association with p53 and p27^{Kip1}. It increases the accumulation of p53 at the posttranslational level and induces cell cycle arrest at the G1 phase via the augmentation of p27^{Kip1} expression in the absence of p53 (Yoo *et al.*, 2005). MRPL41 arrests cell cycle by increasing the p21^{WAF1/CIP1} and p27^{Kip1} levels under the growth inhibitory conditions (Kim *et al.*, 2005) and induces apoptosis by interacting with Bcl-2 (Chintharlapalli *et al.*, 2005). The MRPL41 gene is mapped to chromosome 9q34.3 region, which frequently exhibits a LOH in a wide range of tumors including bladder and lung cancer (Hornigold *et al.*, 1999; Suzuki *et al.*, 1998).

A chimeric protein containing the N-terminal *trans*-activating sequences of L7a and the truncated receptor kinase domain of the *trk* proto-oncogene was identified in breast carcinoma. The chimeric protein is tightly associated with ribosomes in *trk*-2h-transformed cells, and such localization has been suggested to be crucial for oncogene activation (Naora, 1999). Overexpression of L7a is shown in colorectal cancer and prostate carcinomas (Fig. 2). 37LRP/p40 has been identified as a precursor of the metastasis-associated 67 kDa laminin receptor (ribosomal protein SA), whose enhanced expression is associated with tumor invasion and metastatic potential (Naora, 1999). Overexpression of L18 causes to deregulate cell growth through the inhibition of PKR activity (Kumar *et al.*, 1999). PKR provides a control step in the regulation of protein synthesis initiation through phosphorylation of eIF2 α . Kumar *et al.*, (1999) suggested that L18 interacts with PKR, inhibiting both of PKR autophosphorylation and PKR-mediated phosphorylation of eIF2 α . L18 is highly expressed in colon carcinoma (Fig. 2). Thus, L18 may promote protein synthesis and cell growth in certain cancers through the inhibition of PKR activity.

p53 was previously found to be covalently linked to 5.8S rRNA (Fontoura *et al.*, 1992) and to be part of a ribonucleoprotein complex consisting p53, L5 and 5S rRNA (Marechal *et al.*, 1994). In fact, L37, S2 and P1 are highly expressed in human colon carcinoma-derived p53 mutant cell line (Loging and Reisman, 1999). p53 also regulates the expression levels of some RP genes (Budde and Grummt, 1999). Expression of L37 and PO showed the greatest increase in gastrointestinal tumors (Fig. 2). S11 and L7 are highly expressed in carcinoma cells (Kasai *et al.*, 2003). S11 is downregulated in staurosporine-induced apoptotic human breast carcinoma

MCF7 cell line (Nadano *et al.*, 2001). Given that colorectal carcinogenesis is relate to the inhibition of apoptosis (Tsujitani *et al.*, 1996), this result implies that overexpression of S11 might inhibit apoptosis of colon cancer cells. In contrast to S11, the constitutive expression of L7 in Jurkat T-lymphoma cells caused an arrest in G1 phase and induced apoptosis (Neumann and Krawinkel, 1997). S30 is the intriguing protein because this protein is encoded as fusion protein by *fau* gene, a putative tumor suppressor with an ubiquitin-like protein (Michiels *et al.*, 1993). The *fau* gene has an antisense sequence of the *fox* gene in the Finkel-Biskis-Reilly murine sarcoma virus. Thus, expression of the *fox* gene gave the same effects like the antisense *fau* gene and increased the transforming capacity of the virus. Similar results demonstrated that low expression of *fau* protein sensitized cells to carcinogenicity of arsenite (Rossman and Wang, 1999).

Human L3 together with N-myristoyltransferase 2, retinoblastoma-like 2 and cyclin G2 was found to contain the positive correlation with telomerase activity (Bergqvist *et al.*, 2006). Telomerase activity is upregulated during cancer progression in several malignancies and more aggressive tumor type (Usselman *et al.*, 2001), and recent microarray analysis identified that some genes are involved in progression and regulation of telomerase activity and correlated with telomerase activity in several esophageal carcinoma cell lines (Bergqvist *et al.*, 2006). RPs are also thought to be involved in multidrug resistance (MDR) in some tumors. For example, the phosphorylated form of S3a is immunoprecipitated with Bcl-2 from acute myeloblastic leukemia blasts treated by all-trans retinoic acid, and S3a expression level shows correlation with both Bcl-2 and cell growth (Hu *et al.*, 2000) (Table 3). Overexpression of S13 and L23 have been identified in MDR gastric cancer cells suggesting the possibility as the regulators that control the responses to chemotherapy (Shi *et al.*, 2004). In particular, L23 may promote MDR through the regulation of GST-mediated drug-detoxifying system. S28 was upregulated by cisplatin treatment along with EF-1 α (Johnsson *et al.*, 2000), L4 and L5 were induced in the doxorubicin-resistant human colon carcinoma cell line (Bertram *et al.*, 1998), and L6 and L7a were overexpressed in adriamycin-resistant gastric cancer cells (Du *et al.*, 2003; Zhao *et al.*, 2002). Increase of L7a expression was also found in paclitaxel-resistant human head and neck cancer cell lines (Schmidt *et al.*, 2006). L36 and L36aL (L36-related gene) showed the altered expression in cisplatin-resistant human epidermoid carcinoma cells, reflecting their potential association with cisplatin-resistance (Shen *et al.*, 2006) (Table 3).

The myc oncogene family such as c-Myc, l-Myc and n-Myc are amplified, mutated, overexpressed and/or rearranged in many human tumor types. Myc appears to directly regulate ribosome biogenesis through the transcriptional control of RPs (Ruggero and Pandolfi, 2003) (Fig. 3), implying Myc proteins as major regulators of protein synthesis machinery. Among RPs, nine have been identified to be induced by both of n-Myc and c-Myc (Fig. 3).

CONCLUSION AND FUTURE DIRECTIONS

The pathological linkage of translational system to tumorigenesis can be viewed from a few different perspectives. The most straightforward interpretation would be the abnormal promotion of protein synthesis due to the overexpression of translational components, which may result in uncontrolled cell proliferation. Additionally or alternatively, the fidelity of protein synthesis can be affected by the disturbance of translation system, which can be propagated to various diseases including cancer. However, neither of them seems to fully explain the reason for the cancer-specific aberrant expression of specific translational components. In addition, while most of these translational components are featured by their oncogenic properties, quite a few of them work as tumor suppressors. Thus, although the association of translational factors with tumorigenesis may result from their regulatory roles in global or local

Table 3. Ribosomal Proteins Selectively Increased in Drug-Resistant Tumors

RP	Multidrug-Resistant Tumor	References
S3a	Acute myeloblastic leukemia/Cytosine arabinoside, Doxorubicin	Hu <i>et al.</i> , 2000
S13	Gastric cancer cells/Adriamycin, Vincristine, 5-fluorouracil	Shi <i>et al.</i> , 2004
S28	Head and neck cancer cells/Cisplatin	Johnsson <i>et al.</i> , 2000
L4	Colon carcinoma cells/Doxorubicin	Bertram <i>et al.</i> , 1998
L5	Colon carcinoma cells/Doxorubicin	Bertram <i>et al.</i> , 1998
L6	Gastric cancer cells/Adriamycin	Du <i>et al.</i> , 2003, 2005
L7a	Gastric cancer cells/Adriamycin, Head and neck cancer cells/Taxol	Zao <i>et al.</i> , 2002 Schmidt <i>et al.</i> , 2005
L23	Gastric cancer cells/Adriamycin, Vincristine, 5-fluorouracil	Shi <i>et al.</i> , 2004
L36	Epidermoid carcinoma cells/Cisplatin	Shen <i>et al.</i> , 2006
L36aL	Epidermoid carcinoma cells/Cisplatin	Shen <i>et al.</i> , 2006

protein synthesis, it could be due to their noncanonical activities apart from protein synthesis. Since translational system must have emerged early in evolutionary history, the components should have higher chance to adopt additional activities, thereby being linked to diverse processes. Accumulating evidences reveal the intimate correlation between the deregulation and aberration in the multifunctionality of translational components and cancer formation, and suggest that the components of the translational machinery or signal transduction pathways involved in translational initiation could be promising targets for cancer therapy. As an example, inhibitors of the mammalian Target of Rapamycin (mTOR) showed some preliminary activity in clinical trials, giving a hope that we may be able to identify better and more reliable markers or new therapeutic targets for cancer therapy among translational components. So far, the functional promiscuity of the translational factors and their physiological or pathological implications have been studied on individual basis but rarely from systematic point of view. Since we now have sufficient data suggesting the tight association of these factors with tumorigenesis and technical tools to analyze them at more systematic level, it is possible to look into the whole translational machinery as a system to find any physiological or pathological correlation between the components during tumorigenesis. The linkage information of the translational components would provide the new way to determine cancer type and status or suggest promising targets for cancer treatment.

ABBREVIATIONS

AIMPs	= ARS-interacting multifunctional proteins
ALK	= Anaplastic lymphoma kinase
AML	= Acute myeloid leukemia
ARS	= Aminoacyl-tRNA synthetase
CdCl ₂	= Cadmium chloride
CGH	= Comparative genomic hybridization
CHOP	= C/EBP homologous protein
CRS	= Cysteinyl-tRNA synthetase
ECs	= Endothelial cells
eEFs	= Eukaryotic elongation factors
eIFs	= Eukaryotic Initiation factors
eRFs	= Eukaryotic releasing factors
ERK1/2	= Extracellular signal-regulated kinase
EPRS	= Glutamyl-prolyl bifunctional tRNA synthetase
FBP	= FUSE-binding protein
FRS	= Phenylalanyl-tRNA synthetase

GRS	= Glycyl-tRNA synthetase
HNPCC	= Hereditary nonpolyposis colorectal cancer
IFN- γ	= Interferon- γ
IMT	= Inflammatory myofibroblastic tumor
IP-10	= Interferon inducible protein 10
IRS	= Isoleucyl- tRNA synthetase
KRS	= Lysyl-tRNA synthetase
LOH	= Loss of heterozygosity
MDR	= Multidrug resistance
Met-tRNA _i	= Initiator methionyl-tRNA
MIG	= Monokine induced by IFN- γ
miR16-1	= Micro-RNA16-1
MRPL41	= Mitochondrial ribosomal protein L41
MRS	= Methionyl-tRNA synthetase
MSI	= Microsatellite regions
NSCLC	= Non-small cell lung carcinomas
PTC	= Papillary thyroid carcinoma
PTI-1	= Prostate tumor-inducing gene 1
RP	= Ribosomal protein
RRS	= Arginyl-tRNA synthetase
TAM	= Tumor-associated macrophages
TGF- β	= Transforming growth factor- β
TNF- α	= Tumor Necrosis Factor α
TSG	= Tumor suppressor gene
UTR	= Untranslated region
WRS	= Tryptophanyl-tRNA synthetase

REFERENCES

- Abbott, C.M. and Proud, C.G. (2004). Translation factors: in sickness and in health. *Trends Biochem. Sci.* **29**: 25-31.
- Amsterdam, A., Sadler, K.C., Lai, K., Farrington, S., Bronson, R.T., Lees, J.A. and Hopkins, N. (2004). Many ribosomal protein genes are cancer genes in zebrafish. *PLoS Biol.* **2**: E139.
- Baisch, H. (2002). Elevated Ki-67 expression is correlated with TNF α and IFN γ -induced apoptosis in tumour cells. *Cell Prolif.* **35**: 333-42.
- Barnett, G., Jakobsen, A.M., Tas, M., Rice, K., Carmichael, J. and Murray, J. C. (2000). Prostate adenocarcinoma cells release the novel proinflammatory polypeptide EMAP-II in response to stress. *Cancer Res.* **60**: 2850-57.

- Beckwith, J.B. (1983). Wilms' tumor and other renal tumors of childhood: a selective review from the National Wilms' Tumor Study Pathology Center. *Hum. Pathol.* **14**: 481-92.
- Bergqvist, M., Brattstrom, D., Brodin, D., Lindkvist, A., Dahlman-Wright, K., Dreilich, M., Wagenius, G. and Paulsson-Karlsson, Y. (2006). Genes associated with telomerase activity levels in esophageal carcinoma cell lines. *Dis. Esophagus*. **19**: 20-3.
- Bertram, J., Palfner, K., Hiddemann, W. and Kneba, M. (1998). Overexpression of ribosomal proteins L4 and L5 and the putative alternative elongation factor PTI-1 in the doxorubicin resistant human colon cancer cell line LoVoDxR. *Eur. J. Cancer* **34**: 731-6.
- Boon, K., Caron, H.N., van Asperen, R., Valentijn, L., Hermus, M.C., van Sluis, P., Roobeek, I., Weis, I., et al. (2001). N-myc enhances the expression of a large set of genes functioning in ribosome biogenesis and protein synthesis. *EMBO J.* **20**: 1383-93.
- Bottoni, A., Piccin, D., Tagliati, F., Luchin, A., Zatelli, M.C. and degli Uberti, E.C. (2005). miR-15a and miR-16-1 down-regulation in pituitary adenomas. *J. Cell Physiol.* **204**: 280-5.
- Boultood, J., Vidler, C., Lewis, S., Kelly, S., Sheridan, H., Littlewood, T.J., Buckle, V.J. and Wainscoat, J.S. (1994). Molecular mapping of uncharacteristically small 5q deletions in two patients with the 5q syndrome: delineation of the critical region on 5q and identification of a 5q-breakpoint. *Genomics* **19**: 425-32.
- Bridge, J.A., Kanamori, M., Ma, Z., Pickering, D., Hill, D.A., Lydiatt, W., Lui, M.Y., Colleoni, G.W., et al. (2001). Fusion of the ALK gene to the clathrin heavy chain gene, CLTC, in inflammatory myofibroblastic tumor. *Am. J. Pathol.* **159**: 411-5.
- Brito, M., Malta-Vacas, J., Carmona, B., Aires, C., Costa, P., Martins, A.P., Ramos, S., Conde, A.R., et al. (2005). Polyglycine expansions in eRF3/GSPT1 are associated with gastric cancer susceptibility. *Carcinogenesis* **26**: 2046-9.
- Bruhat, A., Jousse, C., Wang, X.Z., Ron, D., Ferrara, M. and Fafournoux, P. (1997). Amino acid limitation induces expression of CHOP, a CCAAT/enhancer binding protein-related gene, at both transcriptional and post-transcriptional levels. *J. Biol. Chem.* **272**: 17588-93.
- Budde, A. and Grummt, I. (1999). p53 represses ribosomal gene transcription. *Oncogene* **18**: 1119-24.
- Buim, M.E., Soares, F.A., Sarkis, A.S. and Nagai, M.A. (2005). The transcripts of SFRP1, CEP63 and EIF4G2 genes are frequently downregulated in transitional cell carcinomas of the bladder. *Oncology* **69**: 445-54.
- Burks, E.A., Bezerra, P.P., Le, H., Gallie, D.R. and Browning, K.S. (2001). Plant initiation factor 3 subunit composition resembles mammalian initiation factor 3 and has a novel subunit. *J. Biol. Chem.* **276**: 2122-31.
- Buttitta, F., Martella, C., Barassi, F., Felicioni, L., Salvatore, S., Rosini, S., D'Antuono, T., Chella, A., et al. (2005). Int6 expression can predict survival in early-stage non-small cell lung cancer patients. *Clin. Cancer Res.* **11**: 3198-204.
- Caraglia, M., Budillon, A., Vitale, G., Lupoli, G., Tagliaferri, P. and Abbuzzese, A. (2000). Modulation of molecular mechanisms involved in protein synthesis machinery as a new tool for the control of cell proliferation. *Eur. J. Biochem.* **267**: 3919-36.
- Castresana, J.S., Barrios, C., Gomez, L. and Kreicbergs, A. (1992). Amplification of the c-myc proto-oncogene in human chondrosarcoma. *Diagn. Mol. Pathol.* **1**: 235-8.
- Chan, Y.L., Diaz, J.J., Denoroy, L., Madjar, J.J. and Wool, I.G. (1996). The primary structure of rat ribosomal protein L10: relationship to a Jun-binding protein and to a putative Wilms' tumor suppressor. *Biochem. Biophys. Res. Commun.* **225**: 952-6.
- Chatterjee, M., Mohapatra, S., Ionan, A., Bawa, G., Ali-Fehmi, R., Wang, X., Nowak, J., Ye, B., et al. (2006). Diagnostic markers of ovarian cancer by high-throughput antigen cloning and detection on arrays. *Cancer Res.* **66**: 1181-90.
- Chen, G., Gharib, T.G., Thomas, D.G., Huang, C.C., Misek, D.E., Kuick, R.D., Giordano, T.J., Iannettoni, M.D., et al. (2003). Proteomic analysis of eIF-5A in lung adenocarcinomas. *Proteomics* **3**: 496-504.
- Cher, M.L., Bova, G.S., Moore, D.H., Small, E.J., Carroll, P.R., Pin, S.S., Epstein, J.I., Isaacs, W.B., et al. (1996). Genetic alterations in untreated metastases and androgen-independent prostate cancer detected by comparative genomic hybridization and allelotyping. *Cancer Res.* **56**: 3091-102.
- Chintharlapalli, S.R., Jasti, M., Malladi, S., Parsa, K.V., Ballesterio, R.P. and Gonzalez-Garcia, M. (2005). BMRP is a Bcl-2 binding protein that induces apoptosis. *J. Cell Biochem.* **94**: 611-26.
- Clemens, M.J. (2004). Targets and mechanisms for the regulation of translation in malignant transformation. *Oncogene* **23**: 3180-8.
- Clemens, M.J. and Bommer, U.A. (1999). Translational control: the cancer connection. *Int. J. Biochem. Cell Biol.* **31**: 1-23.
- Clement, P.M., Henderson, C.A., Jenkins, Z.A., Smit-McBride, Z., Wolff, E.C., Hershey, J.W., Park, M.H. and Johansson, H.E. (2003). Identification and characterization of eukaryotic initiation factor 5A-2. *Eur. J. Biochem.* **270**: 4254-63.
- Coller, H.A., Grandori, C., Tamayo, P., Colbert, T., Lander, E.S., Eisenman, R.N. and Golub, T.R. (2000). Expression analysis with oligonucleotide microarrays reveals that MYC regulates genes involved in growth, cell cycle, signaling, and adhesion. *Proc. Natl. Acad. Sci. USA* **97**: 3260-5.
- Cook, J.R., Dehner, L.P., Collins, M.H., Ma, Z., Morris, S.W., Coffin, C.M. and Hill, D.A. (2001). Anaplastic lymphoma kinase (ALK) expression in the inflammatory myofibroblastic tumor: a comparative immunohistochemical study. *Am. J. Surg. Pathol.* **25**: 1364-71.
- Cools, J., Wlodarska, I., Somers, R., Mentens, N., Pedetour, F., Maes, B., De Wolf-Peeters, C., Pauwels, P., et al. (2002). Identification of novel fusion partners of ALK, the anaplastic lymphoma kinase, in anaplastic large-cell lymphoma and inflammatory myofibroblastic tumor. *Genes Chromosomes Cancer* **34**: 354-62.
- Cruzen, M.E., Bengtsson, U., McMahon, J., Wasmuth, J.J. and Arfin, S.M. (1993). Brief report - assignment of the cysteinyl tRNA synthetase gene (CARS) to 11p15.5. *Genomics* **15**: 692-3.
- Dai, M.S., Zeng, S.X., Jin, Y., Sun, X.X., David, L. and Lu, H. (2004). Ribosomal protein L23 activates p53 by inhibiting MDM2 function in response to ribosomal perturbation but not to translation inhibition. *Mol. Cell Biol.* **24**: 7654-68.
- De Benedetti, A. and Graff, J.R. (2004). eIF-4E expression and its role in malignancies and metastases. *Oncogene* **23**: 3189-99.
- De Benedetti, A. and Harris, A.L. (1999). eIF4E expression in tumors: its possible role in progression of malignancies. *Int. J. Biochem. Cell Biol.* **31**: 59-72.
- Debelenko, L.V., Arthur, D.C., Pack, S.D., Helman, L.J., Schrupp, D.S. and Tsokos, M. (2003). Identification of CARS-ALK fusion in primary and metastatic lesions of an inflammatory myofibroblastic tumor. *Lab. Invest.* **83**: 1255-65.
- DeFatta, R.J., Turbat-Herrera, E.A., Li, B.D., Anderson, W. and De Benedetti, A. (1999). Elevated expression of eIF4E in confined early breast cancer lesions: possible role of hypoxia. *Int. J. Cancer* **80**: 516-22.
- Deniziak, M.A. and Barciszewski, J. (2001). Methionyl-tRNA synthetase. *Acta Biochim. Pol.* **48**: 337-50.
- Dong, Z., Liu, L.H., Han, B., Pincheira, R. and Zhang, J.T. (2004). Role of eIF3 p170 in controlling synthesis of ribonucleotide reductase M2 and cell growth. *Oncogene* **23**: 3790-801.
- Du, J.P., Jin, X.H., Shi, Y.Q., Cao, Y.X., Zhao, Y.Q., Liu, C.J., Yin, F., Hu, W.H., et al. (2003). Differential expression of RPL6/Taxreb107 in drug resistant gastric cancer cell line SGC7901/ADR and its correlation with multiple-drug resistance. *Zhonghua Zhong Liu Za Zhi* **25**: 21-5.
- Dubourg, C., Toutain, B., Helias, C., Henry, C., Lessard, M., Le Gall, J.Y., Le Treut, A. and Guenet, L. (2002). Evaluation of ETF1/eRF1, mapping to 5q31, as a candidate myeloid tumor suppressor gene. *Cancer Genet. Cytogenet.* **134**: 33-7.
- Duyster, J., Bai, R.Y. and Morris, S.W. (2001). Translocations involving anaplastic lymphoma kinase (ALK). *Oncogene* **20**: 5623-37.
- Eberle, J., Fecker, L.F., Bittner, J.U., Orfanos, C.E. and Geilen, C.C. (2002). Decreased proliferation of human melanoma cell lines caused by antisense RNA against translation factor eIF-4A1. *Br. J. Cancer* **86**: 1957-62.
- Eberle, J., Krasagakis, K. and Orfanos, C.E. (1997). Translation initiation factor eIF-4A1 mRNA is consistently overexpressed in human melanoma cells *in vitro*. *Int. J. Cancer* **71**: 396-401.
- Ejiri, S. (2002). Moonlighting functions of polypeptide elongation factor 1: from actin bundling to zinc finger protein R1-associated nuclear localization. *Biosci. Biotechnol. Biochem.* **66**: 1-21.
- Fan, X., Paetau, A., Aalto, Y., Valimaki, M., Sane, T., Poranen, A., Castresana, J.S. and Knuutila, S. (2001). Gain of chromosome 3 and loss of 13q are frequent alterations in pituitary adenomas. *Cancer Genet. Cytogenet.* **128**: 97-103.
- Fingar, D.C., Richardson, C.J., Tee, A.R., Cheatham, L., Tsou, C. and Blenis, J. (2004). mTOR controls cell cycle progression through its cell growth effectors S6K1 and 4E-BP1/eukaryotic translation initiation factor 4E. *Mol. Cell Biol.* **24**: 200-16.

- Fleckner, J., Martensen, P.M., Tolstrup, A.B., Kjeldgaard, N.O. and Justesen, J. (1995). Differential regulation of the human, interferon inducible tryptophanyl-tRNA synthetase by various cytokines in cell lines. *Cytokine* **7**: 70-7.
- Fountoura, B.M., Sorokina, E.A., David, E. and Carroll, R.B. (1992). p53 is covalently linked to 5.8S rRNA. *Mol. Cell Biol.* **12**: 5145-51.
- Forozan, F., Mahlamaki, E.H., Monni, O., Chen, Y., Veldman, R., Jiang, Y., Gooden, G.C., Ethier, S.P., et al. (2000). Comparative genomic hybridization analysis of 38 breast cancer cell lines: a basis for interpreting complementary DNA microarray data. *Cancer Res.* **60**: 4519-25.
- Forus, A., Florenes, V.A., Maelandsmo, G.M., Fodstad, O. and Myklebost, O. (1994). The protooncogene CHOP/GADD153, involved in growth arrest and DNA damage response, is amplified in a subset of human sarcomas. *Cancer Genet. Cytogenet.* **78**: 165-71.
- Francia, G., Man, S., Teicher, B., Grasso, L. and Kerbel, R.S. (2004). Gene expression analysis of tumor spheroids reveals a role for suppressed DNA mismatch repair in multicellular resistance to alkylating agents. *Mol Cell. Biol.* **24**: 6837-49.
- Galasinski, W. and Moldave, K. (1969). Purification of aminoacyltransferase II(translocation factor) from rat liver. *J. Biol. Chem.* **244**: 6527-32.
- Gicquel, C., Raffin-Sanson, M.L., Gaston, V., Bertagna, X., Plouin, P.F., Schlumberger, M., Louvel, A., Luton, J.P., et al. (1997). Structural and functional abnormalities at 11p15 are associated with the malignant phenotype in sporadic adrenocortical tumors: study on a series of 82 tumors. *J. Clin. Endocrinol. Metab.* **82**: 2559-65.
- Gopalkrishnan, R.V., Su, Z.Z., Goldstein, N.I. and Fisher, P.B. (1999). Translational infidelity and human cancer: role of the PTI-1 oncogene. *Int. J. Biochem. Cell Biol.* **31**: 151-62.
- Graff, J.R., Boghaert, E.R., De Benedetti, A., Tudor, D.L., Zimmer, C.C., Chan, S.K. and Zimmer, S.G. (1995). Reduction of translation initiation factor 4E decreases the malignancy of ras-transformed cloned rat embryo fibroblasts. *Int. J. Cancer* **60**: 255-63.
- Gray, N.K. and Wickens, M. (1998). Control of translation initiation in animals. *Annu. Rev. Cell. Dev. Biol.* **14**: 399-458.
- Griffin, C.A., Hawkins, A.L., Dvorak, C., Henkle, C., Ellingham, T. and Perlman, E.J. (1999). Recurrent involvement of 2p23 in inflammatory myofibroblastic tumors. *Cancer Res.* **59**: 2776-80.
- Guan, X.Y., Fung, J.M., Ma, N.F., Lau, S.H., Tai, L.S., Xie, D., Zhang, Y., Hu, L., et al. (2004). Oncogenic role of eIF-5A2 in the development of ovarian cancer. *Cancer Res.* **64**: 4197-200.
- Guan, X.Y., Sham, J.S., Tang, T.C., Fang, Y., Huo, K.K. and Yang, J.M. (2001). Isolation of a novel candidate oncogene within a frequently amplified region at 3q26 in ovarian cancer. *Cancer Res.* **61**: 3806-9.
- Guenet, L., Henry, C., Toutain, B., Dubourg, C., Le Gall, J.Y., David, V. and Le Treut, A. (2000). Eukaryotic translation termination factor gene (ETF1/eRF1) maps at D5S500 in a commonly deleted region of chromosome 5q31 in malignant myeloid diseases. *Cytogenet. Cell Genet.* **88**: 82-6.
- Hake, L.E. and Richter, J.D. (1997). Translational regulation of maternal mRNA. *Biochim. Biophys. Acta* **1332**: M31-8.
- Han, J.M., Lee, M.J., Park, S.G., Lee, S.H., Razin, E., Choi, E.C. and Kim, S. (2006). Hierarchical Network between the Components of the Multi-tRNA Synthetase Complex: Implications for Complex Formation. *J. Biol. Chem.* **281**: 38663-7.
- Hanuske-Abel, H.M., Hanuske, A.R., Slowinska, B. and Popowicz, A.M. (2002). The cell cycle-controlling protein eIF-5A: Identification of functional regions relevant for interaction with mRNA partners. *FASEB J.* **16**: A702.
- Hemmer, S., Wasenius, V.M., Knuutila, S., Franssila, K. and Joensuu, H. (1999). DNA copy number changes in thyroid carcinoma. *Am. J. Pathol.* **154**: 1539-47.
- Henis-Korenblit, S., Shani, G., Sines, T., Marash, L., Shohat, G. and Kimchi, A. (2002). The caspase-cleaved DAP5 protein supports internal ribosome entry site-mediated translation of death proteins. *Proc. Natl. Acad. Sci. USA* **99**: 5400-5.
- Hofmann, W., Reichart, B., Ewald, A., Muller, E., Schmitt, I., Stauber, R.H., Lottspeich, F., Jockusch, B.M., et al. (2001). Cofactor requirements for nuclear export of Rev response element (RRE)- and constitutive transport element (CTE)-containing retroviral RNAs. An unexpected role for actin. *J. Cell Biol.* **152**: 895-910.
- Holland, E.C. (2004). Regulation of translation and cancer. *Cell Cycle* **3**: 452-5.
- Hornigold, N., Devlin, J., Davies, A.M., Aveyard, J.S., Habuchi, T. and Knowles, M.A. (1999). Mutation of the 9q34 gene TSC1 in sporadic bladder cancer. *Oncogene* **18**: 2657-61.
- Hoshino, S., Hosoda, N., Araki, Y., Kobayashi, T., Uchida, N., Funakoshi, Y. and Katada, T. (1999). Novel function of the eukaryotic polypeptide-chain releasing factor 3 (eRF3/GSPT) in the mRNA degradation pathway. *Biochemistry (Mosc)* **64**: 1367-72.
- Hu, R.J., Lee, M.P., Connors, T.D., Johnson, L.A., Burn, T.C., Su, K., Landes, G.M. and Feinberg, A.P. (1997). A 2.5-Mb transcript map of a tumor-suppressing subchromosomal transferable fragment from 11p15.5, and isolation and sequence analysis of three novel genes. *Genomics* **46**: 9-17.
- Hu, Z.B., Minden, M.D., McCulloch, E.A. and Stahl, J. (2000). Regulation of drug sensitivity by ribosomal protein S3a. *Blood* **95**: 1047-55.
- Huang, X.P., Zhao, C.X., Li, Q.J., Cai, Y., Liu, F.X., Hu, H., Xu, X., Han, Y.L., et al. (2006). Alteration of RPL14 in squamous cell carcinomas and preneoplastic lesions of the esophagus. *Gene* **366**: 161-8.
- Ibba, M. and Soll, D. (1999). Quality control mechanisms during translation. *Science* **286**: 1893-97.
- Ichijo, H., Nishida, E., Irie, K., ten Dijke, P., Saitoh, M., Moriguchi, T., Takagi, M., Matsumoto, K., et al. (1997). Induction of apoptosis by ASK1, a mammalian MAPKKK that activates SAPK/JNK and p38 signaling pathways. *Science* **275**: 90-4.
- Imataka, H., Olsen, H.S. and Sonenberg, N. (1997). A new translational regulator with homology to eukaryotic translation initiation factor 4G. *EMBO J.* **16**: 817-25.
- Isola, J.J., Kallioniemi, O.P., Chu, L.W., Fuqua, S.A., Hilsenbeck, S.G., Osborne, C.K. and Waldman, F.M. (1995). Genetic aberrations detected by comparative genomic hybridization predict outcome in node-negative breast cancer. *Am. J. Pathol.* **147**: 905-11.
- Ivakhno, S.S. and Kornelyuk, A.I. (2004). Cytokine-like activities of some aminoacyl-tRNA synthetases and auxiliary p43 cofactor of aminoacylation reaction and their role in oncogenesis. *Exp. Oncol.* **26**: 250-5.
- Jakus, J., Wolff, E.C., Park, M.H. and Folk, J.E. (1993). Features of the spermidine-binding site of deoxyhypusine synthase as derived from inhibition studies. Effective inhibition by bis- and mono-guanylated diamines and polyamines. *J. Biol. Chem.* **268**: 13151-9.
- Jenkins, Z.A., Haag, P.G. and Johansson, H.E. (2001). Human eIF5A2 on chromosome 3q25-q27 is a phylogenetically conserved vertebrate variant of eukaryotic translation initiation factor 5A with tissue-specific expression. *Genomics* **71**: 101-9.
- Johnsson, A., Zeelenberg, I., Min, Y., Hilinski, J., Berry, C., Howell, S.B. and Los, G. (2000). Identification of genes differentially expressed in association with acquired cisplatin resistance. *Br. J. Cancer* **83**: 1047-54.
- Joseph, P., Lei, Y.X. and Ong, T.M. (2004). Up-regulation of expression of translation factors--a novel molecular mechanism for cadmium carcinogenesis. *Mol. Cell Biochem.* **255**: 93-101.
- Joseph, P., Lei, Y.X., Whong, W.Z. and Ong, T.M. (2002). Molecular cloning and functional analysis of a novel cadmium-responsive proto-oncogene. *Cancer Res.* **62**: 703-7.
- Kang, H.A. and Hershey, J.W. (1994). Effect of initiation factor eIF-5A depletion on protein synthesis and proliferation of *Saccharomyces cerevisiae*. *J. Biol. Chem.* **269**: 3934-40.
- Karnik, P., Chen, P., Paris, M., Yeager, H. and Williams, B.R. (1998). Loss of heterozygosity at chromosome 11p15 in Wilms tumors: identification of two independent regions. *Oncogene* **17**: 237-40.
- Kasai, H., Nadano, D., Hidaka, E., Higuchi, K., Kawakubo, M., Sato, T.A. and Nakayama, J. (2003). Differential expression of ribosomal proteins in human normal and neoplastic colorectum. *J. Histochem. Cytochem.* **51**: 567-74.
- Kaziro, Y., Itoh, H., Kozasa, T., Nakafuku, M. and Satoh, T. (1991). Structure and function of signal-transducing GTP-binding proteins. *Annu. Rev. Biochem.* **60**: 349-400.
- Keiper, B.D., Gan, W. and Rhoads, R.E. (1999). Protein synthesis initiation factor 4G. *Int. J. Biochem. Cell Biol.* **31**: 37-41.
- Kerr, B., Mucchielli, M.L., Sigaudy, S., Fabre, M., Saunier, P., Voelckel, M.A., Howard, E., Elles, R., et al. (2003). Is the locus for Costello syndrome on 11p? *J. Med. Genet.* **40**: 469-71.
- Kim, J.Y., Kang, Y.S., Lee, J.W., Kim, H.J., Ahn, Y.H., Park, H., Ko, Y.G. and Kim, S. (2002). p38 is essential for the assembly and stability of macromolecular tRNA synthetase complex: implications for its physiological significance. *Proc. Natl. Acad. Sci. USA* **99**: 7912-6.

- Kim, M.J., Park, B.J., Kang, Y.S., Kim, H. J., Park, J.H. Kang, J. W., Lee, S. W., Han, J. M., *et al.* (2003). Downregulation of fuse-binding protein and c-myc by tRNA synthetase cofactor, p38, is required for lung differentiation. *Nat. Genet.* **34**: 330-6.
- Kim, M.J., Yoo, Y.A., Kim, H.J., Kang, S., Kim, Y.G., Kim, J.S. and Yoo, Y.D. (2005). Mitochondrial ribosomal protein L41 mediates serum starvation-induced cell-cycle arrest through an increase of p21(WAF1/CIP1). *Biochem. Biophys. Res. Commun.* **338**: 1179-84.
- Kim, T., Park, S.G., Kim, J.E., Seol, W., Ko, Y.G. and Kim, S. (2000). Catalytic peptide of human glutamyl-tRNA synthetase is essential for its assembly to the aminoacyl-tRNA synthetase complex. *J. Biol. Chem.* **275**: 21768-72.
- Kjellman, P., Lagercrantz, S., Hoog, A., Wallin, G., Larsson, C. and Zedenius, J. (2001). Gain of 1q and loss of 9q21.3-q32 are associated with a less favorable prognosis in papillary thyroid carcinoma. *Genes Chromosomes Cancer* **32**: 43-9.
- Ko, Y.G., Kang, Y.S., Kim, E.K., Park, S.G. and Kim, S. (2000). Nucleolar localization of human methionyl-tRNA synthetase and its role in ribosomal RNA synthesis. *J. Cell Biol.* **149**: 567-74.
- Ko, Y.G., Park, H. and Kim, S. (2002). Novel regulatory interactions and activities of mammalian tRNA synthetases. *Proteomics* **2**: 1304-10.
- Kraehn, G.M., Scharl, M. and Peter, R.U. (1995). Human malignant melanoma. A genetic disease? *Cancer* **75**: 1228-37.
- Krause, S.W., Rehli, M., Kreutz, M., Schwarzfischer, L., Paulauskis, J.D. and Andreesen, R. (1996). Differential screening identifies genetic markers of monocyte to macrophage maturation. *J. Leukoc. Biol.* **60**: 540-5.
- Kumar, K.U., Srivastava, S.P. and Kaufman, R.J. (1999). Double-stranded RNA-activated protein kinase (PKR) is negatively regulated by 60S ribosomal subunit protein L18. *Mol. Cell Biol.* **19**: 1116-25.
- Kuroki, T., Trapasso, F., Yendamuri, S., Matsuyama, A., Alder, H., Mori, M. and Croce, C.M. (2003). Allele loss and promoter hypermethylation of VHL, RAR-beta, RASSF1A, and FHIT tumor suppressor genes on chromosome 3p in esophageal squamous cell carcinoma. *Cancer Res.* **63**:3724-8.
- Kushner, J.P., Boll, D., Quagliana, J. and Dickman, S. (1976). Elevated methionine-tRNA synthetase activity in human colon cancer. *Proc. Soc. Exp. Biol. Med.* **153**: 273-6.
- Lamberti, A., Caraglia, M., Longo, O., Marra, M., Abbruzzese, A. and Arcari, P. (2004). The translation elongation factor 1A in tumorigenesis, signal transduction and apoptosis: review article. *Amino Acids* **26**: 443-8.
- Lawrence, B., Perez-Atayde, A., Hibbard, M.K., Rubin, B.P., Dal Cin, P., Pinkus, J.L., Pinkus, G.S., Xiao, S., *et al.* (2000). TPM3-ALK and TPM4-ALK oncogenes in inflammatory myofibroblastic tumors. *Am. J. Pathol.* **157**: 377-84.
- Lazard, M., Mirande, M. and Waller, J.P. (1987). Expression of the aminoacyl-tRNA synthetase complex in cultured Chinese hamster ovary cells. Specific depression of the methionyl-tRNA synthetase component upon methionine restriction. *J. Biol. Chem.* **262**: 3982-7.
- Lee, S.W., Cho, B.H., Park, S.G. and Kim, S. (2004). Aminoacyl-tRNA synthetase complexes: beyond translation. *J. Cell Sci.* **117**: 3725-34.
- Lee, Y.S., Han, J.M., Kang, T., Park, Y.I., Kim, H.M. and Kim, S. (2006). Antitumor activity of the novel human cytokine AIMPI in an *in vivo* tumor model. *Mol. Cells* **21**: 213-7.
- Lieber, M., Smith, B., Szakal, A., Nelson-Rees, W. and Todaro, G. (1976). A continuous tumor-cell line from a human lung carcinoma with properties of type II alveolar epithelial cells. *Int. J. Cancer* **17**: 62-70.
- Liu, H., Lo, C.R. and Czaja, M.J. (2002). NF-kappaB inhibition sensitizes hepatocytes to TNF-induced apoptosis through a sustained activation of JNK and c-Jun. *Hepatology* **35**: 772-8.
- Liu, J., Shue, E., Ewalt, K.L. and Schimmel, P. (2004). A new gamma-interferon-inducible promoter and splice variants of an anti-angiogenic human tRNA synthetase. *Nucl. Acids Res.* **32**: 719-27.
- Loging, W.T. and Reisman, D. (1999). Elevated expression of ribosomal protein genes L37, RPP-1, and S2 in the presence of mutant p53. *Cancer Epidemiol. Biomarkers Prev.* **8**: 1011-6.
- Mager, W.H. (1988). Control of ribosomal protein gene expression. *Biochim. Biophys. Acta.* **949**: 1-15.
- Malta-Vacas, J., Aires, C., Costa, P., Conde, A.R., Ramos, S., Martins, A.P., Monteiro, C. and Brito, M. (2005). Differential expression of the eukaryotic release factor 3 (eRF3/GSPT1) according to gastric cancer histological types. *J. Clin. Pathol.* **58**: 621-5.
- Mantovani, A., Bottazzi, B., Colotta, F., Sozzani, S. and Ruco, L. (1992). The origin and function of tumor-associated macrophages. *Immunol. Today* **13**: 265-70.
- Marechal, V., Elenbaas, B., Piette, J., Nicolas, J.C. and Levine, A.J. (1994). The ribosomal L5 protein is associated with mdm-2 and mdm-2-p53 complexes. *Mol. Cell Biol.* **14**: 7414-20.
- Markowitz, S.D. and Roberts, A.B. (1996). Tumor suppressor activity of the TGF-beta pathway in human cancers. *Cytokine Growth Factor Rev.* **7**: 93-102.
- Marten, N.W., Burke, E.J., Hayden, J.M. and Straus, D.S. (1994). Effect of amino acid limitation on the expression of 19 genes in rat hepatoma cells. *FASEB J.* **8**: 538-44.
- Mayeur, G.L., Fraser, C.S., Peiretti, F., Block, K.L. and Hershey, J.W. (2003). Characterization of eIF3k: a newly discovered subunit of mammalian translation initiation factor eIF3. *Eur. J. Biochem.* **270**: 4133-9.
- Mayeur, G.L. and Hershey, J.W. (2002). Malignant transformation by the eukaryotic translation initiation factor 3 subunit p48 (eIF3e). *FEBS Lett.* **514**: 49-54.
- Menssen, A. and Hermeking, H. (2002). Characterization of the c-MYC-regulated transcriptome by SAGE: identification and analysis of c-MYC target genes. *Proc. Natl. Acad. Sci. USA* **99**: 6274-9.
- Meric, F. and Hunt, K.K. (2002). Translation initiation in cancer: a novel target for therapy. *Mol. Cancer Ther.* **1**: 971-9.
- Michiels, L., Van der Rauwelaert, E., Van Hasselt, F., Kas, K. and Merregaert, J. (1993). fau cDNA encodes a ubiquitin-like-S30 fusion protein and is expressed as an antisense sequence in the Finkel-Biskis-Reilly murine sarcoma virus. *Oncogene* **8**: 2537-46.
- Mirande, M. (1991). Aminoacyl-tRNA synthetase family from prokaryotes and eukaryotes: structural domains and their implications. *Prog Nucleic Acid Res. Mol. Biol.* **40**: 95-142.
- Mittelman, F. (1991). Catalog of Chromosome Aberrations in Cancer. edited by Johansson, B. and Mertens, F., John Wiley and Sons.
- Miyaki, M., Iijima, T., Shiba, K., Aki, T., Kita, Y., Yasuno, M., Mori, T., Kuroki, T., *et al.* (2001). Alterations of repeated sequences in 5' upstream and coding regions in colorectal tumors from patients with hereditary nonpolyposis colorectal cancer and Turcot syndrome. *Oncogene* **20**: 5215-8.
- Miyazaki, S., Imatani, A., Ballard, L., Marchetti, A., Buttitta, F., Albertsen, H., Nevanlinna, H.A., Gallahan, D., *et al.* (1997). The chromosome location of the human homolog of the mouse mammary tumor-associated gene INT6 and its status in human breast carcinomas. *Genomics* **46**: 155-8.
- Moldave, K. (1985). Eukaryotic protein synthesis. *Annu. Rev. Biochem.* **54**: 1109-49.
- Morris, S.W., Naeve, C., Mathew, P., James, P.L., Kirstein, M.N., Cui, X. and Witte, D.P. (1997). ALK, the chromosome 2 gene locus altered by the t(2;5) in non-Hodgkin's lymphoma, encodes a novel neural receptor tyrosine kinase that is highly related to leukocyte tyrosine kinase (LTK). *Oncogene* **14**: 2175-88.
- Mosyak, L., Reshetnikova, L., Goldgur, Y., Delarue, M. and Safro, M. G. (1995). Structure of phenylalanyl-tRNA synthetase from *Thermus thermophilus*. *Nat. Struct. Biol.* **2**: 537-47.
- Nadano, D., Aoki, C., Yoshinaka, T., Irie, S. and Sato, T.A. (2001). Electrophoretic characterization of ribosomal subunits and proteins in apoptosis: specific downregulation of S11 in staurosporine-treated human breast carcinoma cells. *Biochemistry* **40**: 15184-93.
- Nakamura, Y., Ito, K. and Isaksson, L.A. (1996). Emerging understanding of translation termination. *Cell* **87**: 147-50.
- Nakao, A., Yoshihama, M. and Kenmochi, N. K. (2004). RPG: the Ribosomal Protein Gene database. *Nucl. Acids Res.* **32**: D168-70
- Naora, H. (1999). Involvement of ribosomal proteins in regulating cell growth and apoptosis: translational modulation or recruitment for extraribosomal activity? *Immunol. Cell Biol.* **77**: 197-205.
- Neumann, F. and Krawinkel, U. (1997). Constitutive expression of human ribosomal protein L7 arrests the cell cycle in G1 and induces apoptosis in Jurkat T-lymphoma cells. *Exp. Cell Res.* **230**: 252-61.
- Nichols, R.C., Pai, S.I., Ge, Q., Targoff, I.N., Plotz, P.H. and Liu, P. (1995). Localization of two human autoantigen genes by PCR screening and in situ hybridization--glycyl-tRNA synthetase locates to 7p15 and alanyl-tRNA synthetase locates to 16q22. *Genomics* **30**: 131-2.
- Nicolaidis, N.C., Kinzler, K.W. and Vogelstein, B. (1995). Analysis of the 5' region of PMS2 reveals heterogeneous transcripts and a novel overlapping gene. *Genomics* **29**: 329-34.

- Nilbert, M., Rydholm, A., Mitelman, F., Meltzer, P.S. and Mandahl, N. (1995). Characterization of the 12q13-15 amplicon in soft tissue tumors. *Cancer Genet Cytogenet.* **83**: 32-6.
- Nupponen, N.N., Hyytinen, E.R., Kallioniemi, A.H. and Visakorpi, T. (1998). Genetic alterations in prostate cancer cell lines detected by comparative genomic hybridization. *Cancer Genet. Cytogenet.* **101**: 53-7.
- Oh, H.S., Kwon, H., Sun, S.K. and Yang, C.H. (2002). QM, a putative tumor suppressor, regulates proto-oncogene c-myc. *J. Biol. Chem.* **277**: 36489-98.
- Okamoto, H., Yasui, K., Zhao, C., Arai, S. and Inazawa, J. (2003). PTK2 and EIF3S3 genes may be amplification targets at 8q23-q24 and are associated with large hepatocellular carcinomas. *Hepatology* **38**: 1242-9.
- Otani, A., Kinder, K., Ewalt, K., Otero, F.J., Schimmel, P. and Friedlander, M. (2002a). Bone marrow-derived stem cells target retinal astrocytes and can promote or inhibit retinal angiogenesis. *Nat. Med.* **8**: 1004-10.
- Otani, A., Slike, B.M., Dorrell, M.L., Hood, J., Kinder, K., Ewalt, K.L., Cheresch, D., Schimmel, P., et al. (2002b). A fragment of human TrpRS as a potent antagonist of ocular angiogenesis. *Proc. Natl. Acad. Sci. USA* **99**: 178-83.
- Paley, E.L., Alexandrova, N. and Smelansky, L. (1995). Tryptophanyl-tRNA synthetase as a human autoantigen. *Immunol. Lett.* **48**: 201-7.
- Paley, E.L., Smelyanski, L., Malinovsky, V., Subbarayan, P.R., Berdichevsky, Y., Posternak, N., Gershoni, J.M., Sokolova, O., et al. (2007). Mapping and molecular characterization of novel monoclonal antibodies to conformational epitopes on NH(2) and COOH termini of mammalian tryptophanyl-tRNA synthetase reveal link of the epitopes to aggregation and Alzheimer's disease. *Mol. Immunol.* **44**: 541-57.
- Palmer, J.L., Masui, S., Pritchard, S., Kalousek, D.K. and Sorensen, P.H. (1997). Cytogenetic and molecular genetic analysis of a pediatric pleomorphic sarcoma reveals similarities to adult malignant fibrous histiocytoma. *Cancer Genet. Cytogenet.* **95**: 141-7.
- Park, B.J., Kang, J.W., Lee, S.W., Choi, S.J., Shin, Y.K., Ahn, Y.H., Choi, Y.H., Choi, D., et al. (2005a). The haploinsufficient tumor suppressor p18 upregulates p53 via interactions with ATM/ATR. *Cell* **120**: 209-21.
- Park, S.G., Ewalt, K.L. and Kim, S. (2005b). Functional expansion of aminoacyl-tRNA synthetases and their interacting factors: new perspectives on housekeepers. *Trends Biochem. Sci.* **30**: 569-74.
- Park, B.J., Oh, Y.S., Park, S.Y., Choi, S.J., Rudolph, C., Schlegelberger, B. and Kim, S. (2006). AIMP3 haploinsufficiency disrupts oncogene-induced p53 activation and genomic stability. *Cancer Res.* **66**: 6913-8.
- Park, M.H., Joe, Y.A. and Kang, K.R. (1998). Deoxyhypusine synthase activity is essential for cell viability in the yeast *Saccharomyces cerevisiae*. *J. Biol. Chem.* **273**: 1677-83.
- Park, S.G., Ewalt, K.L. and Kim, S. (2005b). Functional expansion of aminoacyl-tRNA synthetases and their interacting factors: new perspectives on housekeepers. *Trends Biochem. Sci.* **30**: 569-74.
- Park, S.G., Kang, Y.S., Ahn, Y.H., Lee, S.H., Kim, K.R., Kim, K.W., Koh, G.Y., Ko, Y.G., et al. (2002). Dose-dependent biphasic activity of tRNA synthetase-associating factor, p43, in angiogenesis. *J. Biol. Chem.* **277**: 45243-8.
- Park, S.G., Kim, H.J., Min, Y.H., Choi, E.C., Shin, Y.K., Park, B.J., Lee, S.W. and Kim, S. (2005c). Human lysyl-tRNA synthetase is secreted to trigger proinflammatory response. *Proc. Natl. Acad. Sci. USA* **102**: 6356-61.
- Parker, M.T. and Gerner, E.W. (2002). Polyamine-mediated post-transcriptional regulation of COX-2. *Biochimie* **84**: 815-9.
- Pestova, T.V. and Hellen, C.U. (2001). Functions of eukaryotic factors in initiation of translation. *Cold. Spring. Harb. Symp. Quant. Biol.* **66**: 389-96.
- Rajasekhar, V.K. and Holland, E.C. (2004). Postgenomic global analysis of translational control induced by oncogenic signaling. *Oncogene* **23**: 3248-64.
- Reifenberger, G., Ichimura, K., Reifenberger, J., Elkhouloun, A.G., Meltzer, P.S. and Collins, V.P. (1996). Refined mapping of 12q13-q15 amplicons in human malignant gliomas suggests CDK4/SAS and MDM2 as independent amplification targets. *Cancer Res.* **56**: 5141-5.
- Rho, S.B., Lee, K.H., Kim, J.W., Shiba, K., Jo, Y.J. and Kim, S. (1996). Interaction between human tRNA synthetases involves repeated sequence elements. *Proc. Natl. Acad. Sci. USA* **93**: 10128-33.
- Rhoads, R.E. (1999). Signal transduction pathways that regulate eukaryotic protein synthesis. *J. Biol. Chem.* **274**: 30337-40.
- Rodova, M., Ankilova, V. and Sasfro, M.G. (1999). Human phenylalanyl-tRNA synthetase: cloning, characterization of the deduced amino acid sequences in terms of the structural domains and coordinately regulated expression of the alpha and beta subunits in chronic myeloid leukemia cells. *Biochem. Biophys. Res. Commun.* **255**: 765-73.
- Rosenwald, I.B. (1996). Upregulated expression of the genes encoding translation initiation factors eIF-4E and eIF-2alpha in transformed cells. *Cancer Lett.* **102**: 113-23.
- Rossmann, T.G. and Wang, Z. (1999). Expression cloning for arsenite-resistance resulted in isolation of tumor-suppressor gene cDNA: possible involvement of the ubiquitin system in arsenic carcinogenesis. *Carcinogenesis* **20**: 311-6.
- Rothe, M., Ko, Y., Albers, P. and Wernert, N. (2000). Eukaryotic initiation factor 3 p110 mRNA is overexpressed in testicular seminomas. *Am. J. Pathol.* **157**: 1597-604.
- Ruggiero, D. and Pandolfi, P.P. (2003). Does the ribosome translate cancer? *Nat. Rev. Cancer* **3**: 179-92.
- Salvucci, O., Basik, M., Yao, L., Bianchi, R. and Tosato, G. (2004). Evidence for the involvement of SDF-1 and CXCR4 in the disruption of endothelial cell-branching morphogenesis and angiogenesis by TNF-alpha and IFN-gamma. *J. Leukoc. Biol.* **76**: 217-26.
- Saramaki, O., Willi, N., Bratt, O., Gasser, T.C., Koivisto, P., Nupponen, N.N., Bubendorf, L. and Visakorpi, T. (2001). Amplification of EIF3S3 gene is associated with advanced stage in prostate cancer. *Am. J. Pathol.* **159**: 2089-94.
- Sato, K., Qian, J., Slezak, J.M., Lieber, M.M., Bostwick, D.G., Bergstrahl, E.J. and Jenkins, R.B. (1999). Clinical significance of alterations of chromosome 8 in high-grade, advanced, nonmetastatic prostate carcinoma. *J. Natl. Cancer Inst.* **91**: 1574-80.
- Savinainen, K.J., Linja, M.J., Saramaki, O.R., Tammela, T.L., Chang, G.T., Brinkmann, A.O. and Visakorpi, T. (2004). Expression and copy number analysis of TRPS1, EIF3S3 and MYC genes in breast and prostate cancer. *Br. J. Cancer* **90**: 1041-6.
- Scandurro, A.B., Weldon, C.W., Figueroa, Y.G., Alam, J. and Beckman, B.S. (2001). Gene microarray analysis reveals a novel hypoxia signal transduction pathway in human hepatocellular carcinoma cells. *Int. J. Oncol.* **19**: 129-35.
- Schimmel, P. (1987). Aminoacyl tRNA synthetases: general scheme of structure-function relationships in the polypeptides and recognition of transfer RNAs. *Annu. Rev. Biochem.* **56**: 125-58.
- Schlumberger, M.J. (1998). Papillary and follicular thyroid carcinoma. *N. Engl. J. Med.* **338**: 297-306.
- Schmidt, M., Schler, G., Gruensfelder, P. and Hoppe, F. (2006). Differential gene expression in a paclitaxel-resistant clone of a head and neck cancer cell line. *Eur. Arch. Otorhinolaryngol.* **263**: 127-34.
- Schwarz, M.A., Kandel, J., Brett, J., Li, J., Hayward, J., Schwarz, R.E., Chappey, O., Wautier, J., et al. (1999). Endothelial-monocyte activating polypeptide II, a novel antitumor cytokine that suppresses primary and metastatic tumor growth and induces apoptosis in growing endothelial cells. *J. Exp. Med.* **190**: 341-54.
- Sen, S., Zhou, H., Ripmaster, T., Hittelman, W.N., Schimmel, P. and White, R.A. (1997). Expression of a gene encoding a tRNA synthetase-like protein is enhanced in tumorigenic human myeloid leukemia cells and is cell cycle stage- and differentiation-dependent. *Proc. Natl. Acad. Sci. USA* **94**: 6164-9.
- Shen, D.W., Liang, X.J., Suzuki, T. and Gottesman, M.M. (2006). Identification by functional cloning from a retroviral cDNA library of cDNAs for ribosomal protein L36 and the 10-kDa heat shock protein that confer cisplatin resistance. *Mol. Pharmacol.* **69**: 1383-8.
- Shi, X.P., Yin, K.C., Zimolo, Z.A., Stern, A.M. and Waxman, L. (1996). The subcellular distribution of eukaryotic translation initiation factor, eIF-5A, in cultured cells. *Exp. Cell Res.* **225**: 348-56.
- Shi, Y., Zhai, H., Wang, X., Han, Z., Liu, C., Lan, M., Du, J., Guo, C., et al. (2004). Ribosomal proteins S13 and L23 promote multidrug resistance in gastric cancer cells by suppressing drug-induced apoptosis. *Exp. Cell Res.* **296**: 337-46.
- Steinkasserer, A., Jones, T., Sheer, D., Koettwitz, K., Hauber, J. and Bevec, D. (1995). The eukaryotic cofactor for the human immunodeficiency virus type 1 (HIV-1) rev protein, eIF-5A, maps to chromosome 17p12-p13: three eIF-5A pseudogenes map to 10q23.3, 17q25, and 19q13.2. *Genomics* **25**: 749-52.
- Su, Z., Goldstein, N.I. and Fisher, P.B. (1998). Antisense inhibition of the PTI-1 oncogene reverses cancer phenotypes. *Proc. Natl. Acad. Sci. USA* **95**: 1764-9.

- Summersgill, B., Goker, H., Weber-Hall, S., Huddart, R., Horwich, A. and Shipley, J. (1998). Molecular cytogenetic analysis of adult testicular germ cell tumours and identification of regions of consensus copy number change. *Br. J. Cancer* **77**: 305-13.
- Suzuki, K., Ogura, T., Yokose, T., Nagai, K., Mukai, K., Kodama, T., Nishiwaki, Y. and Esumi, H. (1998). Loss of heterozygosity in the tuberous sclerosis gene associated regions in adenocarcinoma of the lung accompanied by multiple atypical adenomatous hyperplasia. *Int. J. Cancer* **79**: 384-9.
- Taira, H., Ejiri, S. and Shimura, K. (1972). Purification and some properties of G-factor from the silk gland of silkworm. *J. Biochem. (Tokyo)* **72**: 1527-35.
- Thornton, S., Anand, N., Purcell, D. and Lee, J. (2003). Not just for housekeeping: protein initiation and elongation factors in cell growth and tumorigenesis. *J. Mol. Med.* **81**: 536-48.
- Tobiume, K., Matsuzawa, A., Takahashi, T., Nishitoh, H., Morita, K., Takeda, K., Minowa, O., Miyazono, K., et al. (2001). ASK1 is required for sustained activations of JNK/p38 MAP kinases and apoptosis. *EMBO Rep.* **2**: 222-8.
- Tran, N., Bharaj, B.S., Diamandis, E.P., Smith, M., Li, B.D. and Yu, H. (2004). Short tandem repeat polymorphism and cancer risk: influence of laboratory analysis on epidemiologic findings. *Cancer Epidemiol. Biomarkers Prev.* **13**: 2133-40.
- Tsujitani, S., Shirai, H., Tatebe, S., Sugamura, K., Ohfuji, S., Gomyo, Y., Maeta, M., Ito, H., et al. (1996). Apoptotic cell death and its relationship to carcinogenesis in colorectal carcinoma. *Cancer* **77**: 1711-6.
- Turpaev, K.T., Zakhariev, V.M., Sokolova, I.V., Narovlyansky, A.N., Amchenkova, A.M., Justesen, J. and Frolova, L.Y. (1996). Alternative processing of the tryptophanyl-tRNA synthetase mRNA from interferon-treated human cells. *Eur. J. Biochem.* **240**: 732-7.
- Tzima, E., Reader, J.S., Irani-Tehrani, M., Ewalt, K.L., Schwartz, M.A. and Schimmel, P. (2003). Biologically active fragment of a human tRNA synthetase inhibits fluid shear stress-activated responses of endothelial cells. *Proc. Natl. Acad. Sci. USA* **100**: 14903-7.
- Tzima, E., Reader, J.S., Irani-Tehrani, M., Ewalt, K.L., Schwartz, M.A. and Schimmel, P. (2005). VE-cadherin links tRNA synthetase cytokine to anti-angiogenic function. *J. Biol. Chem.* **280**: 2405-8.
- Ubeda, M., Schmitt-Ney, M., Ferrer, J. and Habener, J.F. (1999). CHOP/GADD153 and methionyl-tRNA synthetase (MetRS) genes overlap in a conserved region that controls mRNA stability. *Biochem. Biophys. Res. Commun.* **262**: 31-8.
- Usselman, B., Newbold, M., Morris, A.G. and Nwokolo, C.U. (2001). Telomerase activity and patient survival after surgery for gastric and oesophageal cancer. *Eur. J. Gastroenterol. Hepatol.* **13**: 903-8.
- Uzawa, N., Yoshida, M.A., Oshimura, M. and Ikeuchi, T. (1995). Suppression of tumorigenicity in three different cell lines of human oral squamous cell carcinoma by introduction of chromosome 3p via microcell-mediated chromosome transfer. *Oncogene* **11**: 1997-2004.
- Visakorpi, T. (2003). The molecular genetics of prostate cancer. *Urology* **62**: 3-10.
- Wakasugi, K., Slike, B.M., Hood, J., Ewalt, K.L., Cheresch, D.A. and Schimmel, P. (2002a). Induction of angiogenesis by a fragment of human tyrosyl-tRNA synthetase. *J. Biol. Chem.* **277**: 20124-6.
- Wakasugi, K., Slike, B.M., Hood, J., Otani, A., Ewalt, K.L., Friedlander, M., Cheresch, D.A. and Schimmel, P. (2002b). A human aminoacyl-tRNA synthetase as a regulator of angiogenesis. *Proc. Natl. Acad. Sci. USA* **99**: 173-7.
- Wang, T.W., Lu, L., Wang, D. and Thompson, J.E. (2001). Isolation and characterization of senescence-induced cDNAs encoding deoxyhypusine synthase and eucaryotic translation initiation factor 5A from tomato. *J. Biol. Chem.* **276**: 17541-9.
- Wasenius, V.M., Hemmer, S., Kettunen, E., Knuutila, S., Franssila, K. and Joensuu, H. (2003). Hepatocyte growth factor receptor, matrix metalloproteinase-11, tissue inhibitor of metalloproteinase-1, and fibronectin are up-regulated in papillary thyroid carcinoma: a cDNA and tissue microarray study. *Clin. Cancer Res.* **9**: 68-75.
- Watkins, S.J. and Norbury, C.J. (2004). Cell cycle-related variation in subcellular localization of eIF3e/INT6 in human fibroblasts. *Cell Prolif.* **37**: 149-160.
- Wiesenthal, V., Leutz, A. and Calkhoven, C.F. (2006). A translation control reporter system (TCRS) for the analysis of translationally controlled processes in the vertebrate cell. *Nucl. Acids Res.* **34**: e23.
- Wilkinson, M.F. and Shyu, A.B. (2001). Multifunctional regulatory proteins that control gene expression in both the nucleus and the cytoplasm. *Bioessays*. **23**: 775-787.
- Woese, C. (1998). The universal ancestor. *Proc. Natl. Acad. Sci. USA* **95**: 6854-9.
- Wool, I.G. (1996). Extraribosomal functions of ribosomal proteins. *Trends Biochem. Sci.* **21**: 164-5.
- Wool, I.G., Chan, Y.L. and Gluck, A. (1990). Structure, function, and evolution of mammalian ribosomes. In *The Ribosome. Structure, Function, and Evolution*. American Society for Microbiology.
- Xu, X.L., Wu, L.C., Du, F., Davis, A., Peyton, M., Tomizawa, Y., Maitra, A., Tomlinson, G., et al. (2001). Inactivation of human SRBC, located within the 11p15.5-p15.4 tumor suppressor region, in breast and lung cancers. *Cancer Res.* **61**: 7943-9.
- Yan, R. and Rhoads, R.E. (1995). Human protein synthesis initiation factor eIF-4 gamma is encoded by a single gene (EIF4G) that maps to chromosome 3q27-qter. *Genomics* **26**: 394-8.
- Yoo, Y.A., Kim, M.J., Park, J.K., Chung, Y.M., Lee, J.H., Chi, S.G., Kim, J.S. and Yoo, Y.D. (2005). Mitochondrial ribosomal protein L41 suppresses cell growth in association with p53 and p27Kip1. *Mol. Cell Biol.* **25**: 6603-16.
- Young, M.R. and Wright, M.A. (1992). Myelopoiesis-associated immune suppressor cells in mice bearing metastatic Lewis lung carcinoma tumors: gamma interferon plus tumor necrosis factor alpha synergistically reduces immune suppressor and tumor growth-promoting activities of bone marrow cells and diminishes tumor recurrence and metastasis. *Cancer Res.* **52**: 6335-40.
- Yousem, S.A., Shaw, H. and Cieply, K. (2001). Involvement of 2p23 in pulmonary inflammatory pseudotumors. *Hum. Pathol.* **32**: 428-33.
- Zhang, J., Zheng, S., Gao, Y., Rotolo, J.A., Xiao, Z., Li, C. and Cheng, S. (2004). A partial allelotyping of urothelial carcinoma of bladder in the Chinese. *Carcinogenesis* **25**: 343-7.
- Zhang, L., Pan, X. and Hershey, J.W. (2007). Individual overexpression of five subunits of human translation initiation factor eIF3 promotes malignant transformation of immortal fibroblast cells. *J. Biol. Chem.* **28**: 25790-800.
- Zhao, Y., You, H., Liu, F., An, H., Shi, Y., Yu, Q. and Fan, D. (2002). Differentially expressed gene profiles between multidrug resistant gastric adenocarcinoma cells and their parental cells. *Cancer Lett.* **185**: 211-8.