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Review

The role of protein elongation factor eEF1A2 in ovarian cancer

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Abstract

Frequent gains of chromosome 20q12-13 in ovarian tumors indicate that at least one important oncogene is found at that locus. One of the genes there is *EEF1A2*, which maps to 20q13.3 and encodes protein elongation factor eEF1A2. This review will focus on recent evidence indicating that *EEF1A2* is an important ovarian oncogene and that the protein elongation network can activate tumorigenesis and inhibit apoptosis.

Genetic alterations are the driving force of oncogenesis [1]. In the form of individual nucleotide mutations and small deletions, these changes activate growth-promoting oncogenes and inactivate tumour-suppressors. On the larger chromosomal scale, tumours also possess DNA deletions and amplifications that span hundreds of millions of nucleotides and dozens of genes. The presence of common cytogenetic abnormalities in tumours of the same type implies that these changes are not the simple consequence of tumour development but rather have a causal role in oncogenesis. Considerable effort, therefore, is devoted to characterizing tumour-associated chromosomal abnormalities and identifying the critical gene or genes involved. It is hoped that this will provide new prognostic markers for cancer and lead to the identification of novel therapeutic targets. This review will focus on 20q13, a locus amplified in half of ovarian cancers and protein elongation factor *EEF1A2*, an important oncogene found there.

20q gene amplification and ovarian cancer

The most commonly used techniques to identify tumour-specific chromosomal changes are Comparative Genomic Hybridization (CGH) [2] and Fluorescent In Situ Hybridization (FISH) [3]. Both technologies rely on fluorescence microscopy to quantify cytogenetic alterations in individual tumours. FISH uses a DNA probe homologous to a known chromosomal position to determine the cytogenetic status of that locus. The resolution of FISH is high and is limited only by size of the probe, usually in the 50–200 kb range. Various FISH protocols can assay 24 or more different probes simultaneously [4], but typically only one or two loci are studied. On the other hand, CGH allows the entire chromosomal content of a tumour to be compared to normal DNA in a single experiment without a multitude of mapped probes. CGH has a much lower resolution than FISH, usually 3–5 Mb. CGH and FISH studies on human ovarian tumour samples have revealed common amplifications at 20q, 3q, and 8q [5].

Approximately 50% of ovarian tumours and cell lines have copy number increases in 20q [6–8]. The 20q ovarian amplicon has yet to be precisely sequenced or mapped, but is known to include at least part of 20q12 and 20q13. 20q12-13 amplifications in ovarian tumours are associated with poorer survival and a more aggressive tumour pathology than those with normal 20q copy number [8,9]. 20q12-13 amplifications are also found in a variety of other solid tumours, most notably breast [10] and colorectal cancer [11].

The frequent amplification of 20q12-13 in ovarian tumours argues that at least one of the genes found there is actively promoting tumorigenesis. As of December 2002, the Genome Database (GDB) of the Human Genome Organization (HUGO) has identified 132 genes in 20q12-13 [12]. The protein products of these genes spans a broad range of enzymatic activities that includes kinases, phosphatases, phospholipases, ribosomal proteins and protein translation factors. Moreover, the function of many 20q12-13 genes has yet to be established. It seems unlikely that all 132 genes are important in ovarian cancer. One or more 20q12-13 genes could directly promote tumour growth or two or more genes may cooperate to drive tumour development.

Four genes mapping to 20q12-13, *ZNF217*, *PTP1B*, *STK15*/*BTAK*, and *MYBL2*, seem to be likely candidates as promoters of ovarian tumor development. *ZNF217* encodes a putative transcription factor that can cause the immortalization of human mammary epithelial cells [13,14]. Increased ZNF217 expression increases telomerase activity and stabilizes telomere length [14], but the mechanism by which it does so and the genes whose transcription it directly activates have yet to be identified. *PTB1B* encodes a protein tyrosine phosphatase that, among other substrates, dephosphorylates and activates the Src kinase[15]. Src is the founding member of a tyrosine kinase family that are well-characterized promoters of oncogenesis [16]. STK15/BTK is a centrosome-associated protein kinase that controls centrosome distribution during mitosis [17]. Increased STK15/BTAK expression can promote the tumorigenicity of multiple mouse and rodent cell lines and its ectopic expression leads to centrosomal defects and aneuploidy [17]. MYBL2 is a homologue of the v-myb avian oncogene whose enforced expression can transform avian and mammalian cell lines [18]. A plausible case can be made that all of these genes may contribute in some way to ovarian tumor development. However, the actual role that each of these proteins play in ovarian tumorigenesis have yet to be ascertained.

Protein elongation factor eEF1A2

My lab has focused on attention on another gene in the 20q amplicon, *EEF1A2*. *EEF1A2* maps to 20q13.3 [19] and encodes protein elongation factor eEF1A2. By convention, *EEF1A2* refers to the human gene and eEF1A2 refers to the protein product. eEF1A2 is a protein translation factor. Protein translation is conceptually divided into three stages: initiation, elongation, and termination. Comprehensive reviews of each stage are found elsewhere [20–22]. Simply, the assembly of ribosomal subunits and the initiator methionine tRNA at the mRNA's AUG is termed initiation. The sequential addition of amino acids to the methionine and the translocation of the ribosome along the mRNA is described as elongation. At termination, the ribosomal subunits and the newly formed polypeptide dissociate from the mRNA. Each stage of protein translation is controlled by multimeric protein factors, eIF (eukaryotic Initiation Factor), eEF (eukaryotic Elongation Factor) and eRF (eukaryotic Release Factor), that respectively regulate initiation, elongation and termination.

eEF1A2 is one of two isoforms (eEF1A1 and eEF1A2) of eukaryotic elongation factor 1 alpha (eEF1A or eEF1α). Both eEF1A proteins directly bind amino acylated tRNA and direct its association with the ribosome and mRNA codon [21]. The two human isoforms share>90% sequence identity and have essentially the same function during protein translation. The expression patterns of the two isoforms are markedly different, however. In humans, eEF1A1 is expressed ubiquitously whereas eEF1A2 expression is restricted to the heart, brain, and skeletal muscle [23]. The functional significance of the tissue-specific expression pattern of eEF1A2 has yet to be determined.

At first blush, the seemingly banal function of eEF1A2 does not appear to make it a likely candidate as an ovarian cancer oncogene. Our lab first became interested in eEF1A2 because of the Wasted mouse (*wst*/*wst*). First described by Shultz and collaborators in 1982 [24], Wasted is a spontaneous recessive mutation in HRS/J mice that leads to immuno-deficiency, neural abnormalities and progressive muscular wasting. Wasted mice die at approximately 30 days of age [24]. Cells derived from Wasted mice show higher sensitivity to DNA damage-induced cell death than controls and their lymphoid organs are smaller and show dramatically elevated levels of apoptosis compared to their littermates [25,26]. The Wasted phenotype results from a deletion of the promoter and first exon of the mouse *Eef1A2* gene, which is the human *EEF1A2* homologue [27]. The mouse gene nomenclature differs from that of the human. Since a homozygous deletion of *Eef1A2* leads to increased apoptosis in Wasted mice [26], we reasoned that *EEF1A2* amplification in ovarian cancers might lead to an inhibition of apoptosis, a process that could plausibly contribute to neoplastic progression. Moreover, the mapping of *EEF1A2* to 20q13 [19] provided another rationale for investigating it as a potential oncogene in ovarian cancer.

EEF1A2, an unusual oncogene

Historically, for a gene to be considered a tumour-promoting oncogene, it should be hyper-activated or hyper-expressed in primary human cancers and have the capacity to "transform" rodent cells cultured *in vitro*. Transforming ability means that expression of the gene can cause fibroblast cells to grow in an anchorage-independent manner and to form dome-like structures in tissue culture called foci. This definition of an oncogene is somewhat

arbitrary and by no means absolute, but most generally accepted oncogenes have these properties.

We have found that *EEF1A2* is increased in copy number in about one third of primary ovarian tumors [28]. eEF1A2 mRNA is not detectable in normal ovarian epithelium but about a third of human ovarian tumours have measurable *EEF1A2* mRNA [28]. eEF1A1 expression, on the other hand, is not detectably changed between normal and ovarian tumour samples. Importantly, ectopic expression of wild-type eEF1A2 transforms mouse and rat fibroblasts and allows them to grow as tumors when xenografted into mice. When eEF1A2 is expressed in a human ovarian cell line that does not express eEF1A2, the eEF1A2-expressing line is more tumorigenic than that of its parental control [28]. *EEF1A2* amplification, increased mRNA expression and its transforming potential indicate that eEF1A2 is an important ovarian cancer oncogene. It is unlikely that *EEF1A2* is the only oncogene in the 20q amplicon important to ovarian cancer. As summarized above, there are many potential oncogenes there and perhaps amplification of all of them is necessary for tumour development. Moreover, it has yet to be demonstrated whether eEF1A2 can directly promote tumorigenesis in transgenic mouse models of ovarian cancer, but this is a research avenue that our lab is actively pursuing.

Protein translation factors as oncogenes

Tatsuka and colleagues were the first to implicate the protein elongation machinery in cell transformation [29]. They screened a mouse expression library for genes that would enhance the rate of spontaneous and chemically-induced transformation of mouse and hamster fibroblasts. One of the genes they identified was *Eef1A1*, the mouse homologue of human *EEF1A1*, which increased the transforming ability of 3-methylcholanthrene and ultraviolet light [29]. The first report linking human *EEF1A1* to cancer was work from Paul Fisher's group at Columbia University, who identified a gene expressed in primary prostate carcinomas but not in normal prostate [30]. They named this gene PTI-1 for prostate tumor inducing gene 1. Expression of PTI-1 in non-tumorigenic prostate cell lines made these cells tumorigenic in nude mice. When sequenced, PTI-1 turned out to be a fusion between a *Mycoplasma hyopheumoniae* 23S ribosomal RNA gene and a mutated form of human *EEF1A1*. This work raised the possibility that the fusion of a gene from an infectious agent (*Mycoplasma*) and a human gene could have created a novel prostate cancer oncogene. However, the unusual composition of PTI-1 raised the possibility that PTI-1 was a laboratory epiphenomenon. PTI-1 has been detected in other tumour cell lines [31,32] but the relevance of PTI-1 to prostate and other cancers still remains an unresolved, albeit intriguing, issue.

eEF1A1 and eEF1A2 are not the only protein translation factors implicated in cancer. eIF4E, an mRNA cap-binding involved in protein initiation, transforms NIH 3T3 cells and allows them to grow as tumors in mice [33]. *EIF4E*, the human eIF4E gene, maps to 4q21, a locus amplified in the vast majority of non-small cell lung cancers [34] and some breast tumors [35]. Furthermore, abnormally high eIF4E expression is observed in many solid tumours [36–39].

eEF1A proteins regulate apoptosis

The elevated apoptosis in the eEF1A2-deficient Wasted mice [26] is at least consistent with the idea that eEF1A2, and the related eEF1A1, might be inhibitors of apoptosis. Consistent with this idea, eEF1A1 was recently cloned in a screen for genes that protect against apoptosis induced by IL-3 withdrawal [40]. Furthermore, ectopic rat eEF1A2 expression can protect muscle cells from caspase-3-induced apoptosis [41]. These results imply that eEF1A1 and eEF1A2 both inhibit apoptosis. Interestingly, a recent report suggests that the acquisition of cisplatin resistance in a human head and neck cancer cell line was associated with increased eEF1A1 expression [42]. Increased expression of eEF1A1, relative to normal tissue, occurs in melanomas, tumors of the pancreas, breast, lung, prostate and colon [42–47]. Given this high tumour-specific expression of eEF1A1 and eEF1A2, it is tempting to speculate that their expression might contribute to resistance to anti-cancer therapy, especially in ovarian cancer. It is also intriguing to think that the ability of both eEF1A1 and eEF1A2 to enhance cell growth and tumorigenesis could be related to their ability to inhibit apoptosis.

How does it work?

How might the ectopic expression of an elongation factor enhance cell growth and inhibit apoptosis? eEF1A proteins could specifically upregulate the production of proteins that activate cell replication and growth such as Ras or Myc. It is hard to understand, however, how eEF1A2 could upregulate the production of specific proteins. The coding region of an mRNA is the only place where an elongation factor interacts with a functional ribosome/mRNA complex. A protein's mRNA coding region presumably lacks any information other than that for the polypeptide's primary amino acid sequence. Thus, it seems unlikely that proteins with oncogenic potential could carry some kind of specific information or secondary structure in their coding region that would make them specific candidates for elongation activation in the presence of high amounts of eEF1A2.

On the other hand, increased eEF1A1 and eEF1A2 expression may not specifically increase the production of particular proteins but rather lead to an overall increase in protein translation. An increase in bulk protein synthesis

may enhance cell replication because cell division requires sufficient protein production to fulfill the metabolic and size requirements of two new daughter cells [48]. Increasing bulk protein abundance may decrease the time required to translate the overall mass of proteins necessary for cell division. If this is the case, then it would be expected that anything increasing protein translation rates would be predicted to be oncogenic. The reverse is certainly true, and inhibitors of protein translation are universally and highly toxic to cells and organisms.

Alternatively, eEF1A proteins may enhance tumorigenesis independent of the protein translation network. eEF1A proteins are known to associate with actin and tubulin, and ectopic eEF1A expression can decrease the length of actin filaments and tubulin microtubules [49,50]. Perhaps, the ability of eEF1A to alter cell structure somehow contributes to a neoplastic phenotype. However, the physiological importance of the association of eEF1A with the cytoskeleton has yet to be clearly established, so it is unclear how eEF1A1 and eEF1A2 might control cell growth though cytoskeletal interaction.

An eEF1A2-centered perspective on ovarian cancer

While we have established that the eEF1A2 is genetically amplified and overexpressed in ovarian tumours and has oncogenic properties, it has yet to be shown whether eEF1A2 expression can directly cause ovarian or other cancers in animals. Furthermore, we have yet to understand the mechanism by which eEF1A2 promotes tumorigenesis. In the absence of mechanistic insight, there are still important issues that need addressing with regard to eEF1A2 and ovarian cancer. Firstly, is *EEF1A2* copy number or eEF1A2 protein expression an ovarian cancer prognostic factor? Secondly, is eEF1A2 a suitable target for anticancer therapy? It could be argued that because all cells require protein synthesis, inhibitors of protein elongation would have substantial cytotoxic effects on normal tissues. However, rapidly growing tumor tissue may be more sensitive to decreases in protein synthesis than normal tissue because of the added burdens of an increased proliferation rate. A similar relationship has been exploited in the use of DNA-damaging agents in cancer treatment. Indeed, Rapamycin, an inhibitor of eIF4E-dependent protein initiation, is now being tested in breast cancer [51]. Perhaps, when eEF1A2-inactivating agents are found, they might have efficacy in ovarian cancer.

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References

1. Hahn WC and Weinberg RA: **Modelling the molecular circuitry of cancer.** *Nat Rev Cancer* 2001, **2:**331-341.
2. Kallioniemi A, Kallioniemi OP, Sudar D, Rutovitz D, Gray JW, Waldman F and Pinkel D: **Comparative genomic hybridization for molecular cytogenetic analysis of solid tumors.** *Science* 1992, **258:**818-821.
3. Buckle VJ and Kearney L: **New methods in cytogenetics.** *Curr Opin Genet Dev* 1994, **4:**374-382.
4. Lichter P: **Multicolor FISHing: what's the catch?** *Trends Genet* 1997, **13:**475-479.
5. Wang N: **Cytogenetics and molecular genetics of ovarian cancer.** *Am J Med Genet* 2002, **115:**157-163.
6. Iwabuchi H, Sakamoto M, Sakunaga H, Ma YY, Carcangiu ML, Pinkel D, Yang-Feng TL and Gray JW: **Genetic analysis of benign, low-grade, and high-grade ovarian tumors.** *Cancer Res* 1995, **55:**6172-6180.
7. Sonoda G, Palazzo J, du Manoir S, Godwin AK, Feder M, Yakushiji M and Testa JR: **Comparative genomic hybridization detects frequent overrepresentation of chromosomal material from 3q26, 8q24, and 20q13 in human ovarian carcinomas.** *Genes Chromosomes Cancer* 1997, **20:**320-328.
8. Tanner MM, Grenman S, Koul A, Johannsson O, Meltzer P, Pejovic T, Borg A and Isola JJ: **Frequent amplification of chromosomal region 20q12-q13 in ovarian cancer.** *Clin Cancer Res* 2000, **6:**1833-1839.
9. Diebold J, Mosinger K, Peiro G, Pannekamp U, Kaltz C, Baretton GB, Meier W and Lohrs U: **20q13 and cyclin D1 in ovarian carcinomas. Analysis by fluorescence in situ hybridization.** *J Pathol* 2000, **190:**564-571.
10. Hodgson JG, Chin K, Collins C and Gray JW: **Genome amplification of chromosome 20 in breast cancer.** *Breast Cancer Res Treat* 2003, **78:**337-345.
11. Schlegel J, Stumm G, Scherthan H, Bocker T, Zirngibl H, Ruschoff J and Hofstadter F: **Comparative genomic in situ hybridization of colon carcinomas with replication error.** *Cancer Res* 1995, **55:**6002-6005.
12. [http://www.gdb.org/gdbreports/GeneByChromosome.20.alpha.html].
13. Collins C, Rommens JM, Kowbel D, Godfrey T, Tanner M, Hwang SI, Polikoff D, Nonet G, Cochran J, Myambo K and et al: **Positional cloning of ZNF217 and NABC1: genes amplified at 20q13.2 and overexpressed in breast carcinoma.** *Proc Natl Acad Sci U S A* 1998, **95:**8703-8708.
14. Nonet GH, Stampfer MR, Chin K, Gray JW, Collins CC and Yaswen P: **The ZNF217 gene amplified in breast cancers promotes immortalization of human mammary epithelial cells.** *Cancer Res* 2001, **61:**1250-1254.
15. Bjorge JD, Pang A and Fujita DJ: **Identification of protein-tyrosine phosphatase 1B as the major tyrosine phosphatase activity capable of dephosphorylating and activating c-Src in several human breast cancer cell lines.** *J Biol Chem* 2000, **275:**41439-41446.
16. Courtneidge SA: **Protein tyrosine kinases, with emphasis on the Src family.** *Semin Cancer Biol* 1994, **5:**239-246.
17. Zhou H, Kuang J, Zhong L, Kuo WL, Gray JW, Sahin A, Brinkley BR and Sen S: **Tumour amplified kinase STK15/BTAK induces centrosome amplification, aneuploidy and transformation.** *Nat Genet* 1998, **20:**189-193.
18. Lipsick JS and Wang DM: **Transformation by v-Myb.** *Oncogene* 1999, **18:**3047-3055.
19. Lund A, Knudsen SM, Vissing H, Clark B and Tommerup N: **Assignment of human elongation factor 1alpha genes: EEF1A maps to chromosome 6q14 and EEF1A2 to 20q13.3.** *Genomics* 1996, **36:**359-361.
20. Hershey JW and Merrick WC: **The Pathway and Mechansim of Initiation of Protein Synthesis.** *New York, Cold Spring Harbor Laboraotry Press*; 2000:33-88.
21. Browne GJ and Proud CG: **Regulation of peptide-chain elongation in mammalian cells.** *Eur J Biochem* 2002, **269:**5360-5368.
22. Kisselev L, Ehrenberg M and Frolova L: **Termination of translation: interplay of mRNA, rRNAs and release factors?** *EMBO J* 2003, **22:**175-182.
23. Knudsen SM, Frydenberg J, Clark BF and Leffers H: **Tissue-dependent variation in the expression of elongation factor-1 alpha isoforms: isolation and characterisation of a cDNA encoding**

a novel variant of human elongation-factor 1 alpha. *Eur J Biochem* 1993, **215:**549-554.
24. Shultz LD, Sweet HO, Davisson MT and Coman DR: **'Wasted', a new mutant of the mouse with abnormalities characteristic to ataxia telangiectasia.** *Nature* 1982, **297:**402-404.
25. Padilla M, Libertin C, Krco C and Woloschak GE: **Radiation sensitivity of T-lymphocytes from immunodeficient "wasted" mice.** *Cell Immunol.* 1990, **130:**186-194.
26. Potter M, Bernstein A and Lee JM: **The wst gene regulates multiple forms of thymocyte apoptosis.** *Cell Immunol* 1998, **188:**111-117.
27. Chambers DM, Peters J and Abbott CM: **The lethal mutation of the mouse wasted (wst) is a deletion that abolishes expression of a tissue-specific isoform of translation elongation factor 1alpha, encoded by the Eef1a2 gene.** *Proc Natl Acad Sci U S A* 1998, **95:**4463-4468.
28. Anand N, Murthy S, Amann G, Wernick M, Porter LA, Cukier IH, Collins C, Gray JW, Diebold J and Demetrick DJ *et al.*: **Protein elongation factor EEF1A2 is a putative oncogene in ovarian cancer.** *Nat Genet* 2002, **31:**301-305.
29. Tatsuka M, Mitsui H, Wada M, Nagata A, Nojima H and Okayama H: **Elongation factor-1 alpha gene determines susceptibility to transformation.** *Nature* 1992, **359:**333-336.
30. Shen R, Su ZZ, Olsson CA and Fisher PB: **Identification of the human prostatic carcinoma oncogene PTI-1 by rapid expression cloning and differential RNA display.** *Proc Natl Acad Sci U S A* 1995, **92:**6778-6782.
31. Beyer-Sehlmeyer G, Hiddemann W, Wormann B and Bertram J: **Suppressive subtractive hybridisation reveals differential expression of serglycin, sorcin, bone marrow proteoglycan and prostate-tumour-inducing gene 1 (PTI-1) in drug-resistant and sensitive tumour cell lines of haematopoetic origin.** *Eur J Cancer* 1999, **35:**1735-1742.
32. Ohnami S, Matsumoto N, Nakano M, Aoki K, Nagasaki K, Sugimura T, Terada M and Yoshida T: **Identification of genes showing differential expression in antisense K-ras-transduced pancreatic cancer cells with suppressed tumorigenicity.** *Cancer Res* 1999, **59:**5565-5571.
33. Lazaris-Karatzas A, Montine KS and Sonenberg N: **Malignant transformation by a eukaryotic initiation factor subunit that binds to mRNA 5' cap.** *Nature* 1990, **345:**544-547.
34. Balsara BR, Sonoda G, du Manoir S, Siegfried JM, Gabrielson E and Testa JR: **Comparative genomic hybridization analysis detects frequent, often high-level, overrepresentation of DNA sequences at 3q, 5p, 7p, and 8q in human non-small cell lung carcinomas.** *Cancer Res* 1997, **57:**2116-2120.
35. Sorrells DL, Meschonat C, Black D and Li BD: **Pattern of amplification and overexpression of the eukaryotic initiation factor 4E gene in solid tumor.** *J Surg Res* 1999, **85:**37-42.
36. Li BD, Liu L, Dawson M and De Benedetti A: **Overexpression of eukaryotic initiation factor 4E (eIF4E) in breast carcinoma.** *Cancer* 1997, **79:**2385-2390.
37. Berkel HJ, Turbat-Herrera EA, Shi R and De Benedetti A: **Expression of the translation initiation factor eIF4E in the polyp-cancer sequence in the colon.** *Cancer Epidemiol Biomarkers Prev* 2001, **10:**663-666.
38. Nathan CA, Sanders K, Abreo FW, Nassar R and Glass J: **Correlation of p53 and the proto-oncogene eIF4E in larynx cancers: prognostic implications.** *Cancer Res* 2000, **60:**3599-3604.
39. Haydon MS, Googe JD, Sorrells DS, Ghali GE and Li BD: **Progression of eIF4e gene amplification and overexpression in benign and malignant tumors of the head and neck.** *Cancer* 2000, **88:**2803-2810.
40. Talapatra S, Wagner JD and Thompson CB: **Elongation factor-1 alpha is a selective regulator of growth factor withdrawal and ER stress-induced apoptosis.** *Cell Death Differ* 2001, **9:**856-861.
41. Ruest LB, Marcotte R and Wang E: **Peptide elongation factor eEF1A-2/S1 expression in cultured differentiated myotubes and its protective effect against caspase-3-mediated apoptosis.** *J Biol Chem* 2002, **277:**5418-5425.
42. Johnsson A, Zeelenberg I, Min Y, Hilinski J, Berry C, Howell SB and Los G: **Identification of genes differentially expressed in association with acquired cisplatin resistance.** *Br J Cancer* 2000, **83:**1047-1054.
43. Grant AG, Flomen RM, Tizard ML and Grant DA: **Differential screening of a human pancreatic adenocarcinoma lambda gt11 expression library has identified increased transcription of elongation factor EF-1 alpha in tumour cells.** *Int J Cancer* 1992, **50:**740-745.
44. Zhang L, Zhou W, Velculescu VE, Kern SE, Hruban RH, Hamilton SR, Vogelstein B and Kinzler KW: **Gene expression profiles in normal and cancer cells.** *Science* 1997, **276:**1268-1272.
45. Xie D, Jauch A, Miller CW, Bartram CR and Koeffler HP: **Discovery of over-expressed genes and genetic alterations in breast cancer cells using a combination of suppression subtractive hybridization, multiplex FISH and comparative genomic hybridization.** *Int J Oncol* 2002, **21:**499-507.
46. Mohler JL, Morris TL, Ford OH, Alvey RF, Sakamoto C and Gregory CW: **Identification of differentially expressed genes associated with androgen-independent growth of prostate cancer.** *Prostate* 2002, **51:**247-255.
47. de Wit NJ, Burtscher HJ, Weidle UH, Ruiter DJ and van Muijen GN: **Differentially expressed genes identified in human melanoma cell lines with different metastatic behaviour using high density oligonucleotide arrays.** *Melanoma Res* 2002, **12:**57-69.
48. Johnston GC, Pringle JR and Hartwell LH: **Coordination of growth with cell division in the yeast Saccharomyces cerevisiae.** *Exp Cell Res* 1977, **105:**79-98.
49. Condeelis J: **Elongation factor 1 alpha, translation and the cytoskeleton.** *Trends Biochem Sci* 1995, **20:**169-170.
50. Shiina N, Gotoh Y, Kubomura N, Iwamatsu A and Nishida E: **Microtubule severing by elongation factor 1 alpha.** *Science* 1994, **266:**282-285.
51. Huang S and Houghton PJ: **Inhibitors of mammalian target of rapamycin as novel antitumor agents: from bench to clinic.** *Curr Opin Investig Drugs* 2002, **3:**295-304.