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Review

Role of Oncogenes and Tumor-suppressor Genes in Carcinogenesis: A Review

EMMANUEL N. KONTOMANOLIS[1], ANTONIOS KOUTRAS[2], ATHANASIOS SYLLAIOS[3], DIMITRIOS SCHIZAS[3], AIKATERINI MASTORAKI[3], NIKOLAOS GARMPIS[3], MICHAIL DIAKOSAVVAS[2], KYVELI ANGELOU[2], GEORGIOS TSATSARIS[1], ATHANASIOS PAGKALOS[4], THOMAS NTOUNIS[2] and ZACHARIAS FASOULAKIS[2]

[1]Department of Obstetrics and Gynecology, Democritus University of Thrace, Alexandroupolis, Greece;
[2]First Department of Obstetrics and Gynecology,
Alexandra Maternity Hospital, National and Kapodistrian University of Athens, Athens, Greece;
[3]First Department of Surgery, Laikon General Hospital, National and
Kapodistrian University of Athens, Athens, Greece;
[4]Department of Obstetrics and Gynecology, General Hospital of Xanthi, Xanthi, Greece

Abstract. *Cancer is a medical condition which has a molecular basis. Proto-oncogenes are the first regulatory factors of this biological process. They act in transmitting signals, resulting as growth factors. Modifications of these genes, called oncogenes, lead to the appearance of cancer cells. The activation process leading to proto-oncogenes are chromosomal translocation, point mutation, and gene amplification. Concerning the clonal theory of oncogenesis, it is believed that a tumor starts from a cell. Furthermore, there is close association between tumor development and inhibition of apoptosis or programmed cell death, providing cell immortality. Angiogenesis and angiogenic factors found to be expressed in tumors and may play a key role in tumor formation and development. Tumor-suppressor genes block the growth of cancer and contribute to the normal development of cells. This article highlights the evidence that neoplasms develop as the after-effect of the increase of acquired and physical genetic variations in proto-oncogenes and tumor-suppressor genes; these form a target group in the cells of neoplasms. Tumor formation and development are characterized by individual processes, working synergistically, and an understanding of each individual process may provide a better basis for further anticancer research.*

Correspondence to: Nikolaos Garmpis, First Department of Surgery, Laikon General Hospital, National and Kapodistrian University of Athens, Athens, 11524, Greece. E-mail: antoniskoy@yahoo.gr

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Human cancer is a disease with a molecular basis and today we know many of the genes involved in carcinogenesis. Cancer is characterized by specific attributes, *e.g.* abnormal signal transduction, which can lead to cell multiplication that cannot be controlled; metastasis, apoptosis loss, and angiogenesis. Neoplasms develop as the after-effect of an increase of acquired and physical genetic variations in proto-oncogenes, tumor-suppressor genes and DNA-repair genes (1, 2).

Oncogenes and Cancer

In the normal cell, there are proto-oncogenes which are key regulatory factors of biological processes. Proto-oncogenes may function as growth factors, transducers of cellular signals and nuclear transcription factors (Table I). Mammalian and avian genomes contain a range of proto-oncogenes which control normal cell differentiation and proliferation (3). Changes to these genes that influence either the control of their behavior or the way that their encoded proteins are structured can show up in cancer cells as enacted oncogenes. When such oncogenes are formed, they go on to drive cell multiplication and assume a pivotal role in the pathogenesis of cancer. The physical mutations that lead to the activation of proto-oncogenes can be distinguished into two types: those that lead to differences in the structure of the encoded protein and those that cause deregulation of protein expression (4, 5). Mutations influencing structure include point mutations of *RAS* proto-oncogenes and chromosomal translocations that produce hybrid genes, such as the Philadelphia translocation (*BRC-ABL*). Increased expression occurs in human tumors *via* the amplification of genes or translocation of chromosomes, such as those that

Table I. *Proto-oncogenes with a role in the regulation of cell growth signals (3-8).*

Role in mitogen signal transduction	Proto-oncogene	Encoded protein	Function of the proto-oncogene product
Growth factor receptors	*ERBB*	Receptor tyrosine-protein kinase	Cell membrane receptor for interleukin
	ERBB2	Receptor tyrosine-protein kinase ERBB2	Growth factor receptor
	FMS	Tyrosine-protein kinase transforming protein fms	Receptor for CSF1
	MET	Tyrosine-protein kinase Met	Receptor for HGF
	RET	Receptor tyrosine kinase	Receptor for GDNF
Growth factors	*SIS*	Platelet-derived growth factor (PDGF)	β-Chain for PDGF
	HST	Homogentisate solanesyltransferase, chloroplastic	Growth factor of FGF
	FGF5	Fibroblast growth factor 5	Growth factor for fibroblasts
Transduction factors with kinase action	*ABL*	Tyrosine-protein kinase ABL	Tyrosine kinase
	SRC	Tyrosine-protein kinase Src	Tyrosine kinase
	RAS	RAS small GTPase,	G-Protein
	SOS	Guanine nucleotide exchange factors	Exchange factor of nucleotide of guanine
	CDK4	Cyclin dependent kinase 4 protein	Cyclin-dependent kinase
Nuclear transcription factors	*FOS*	Leucine zipper protein	Transcription factor
	JUN	Activator protein 1	Transcription factor
	MYC	MYC transcription factor protein	Transcription factor
	GLI	GLI family zinc finger 1	Transcription factor
	TTG	Tissue transglutaminase	Transcription factor
	ERBA	Thyroid hormone receptor alpha	Member of the steroid receptor family
Anti-apoptotic factors	*BCL2*	B-Cell lymphoma 2 protein	Inhibition of apoptosis
Binding to protein P53	*MDM2*	Mouse double minute 2 homolog	Transcriptional regulation

EGF: Epidermal growth factor; CSF1: inducing factor of macrophage-1 colonization; HGF: hepatocyte growth factor; FGF: fibroblast growth factor; GDNF: glial-derived necrotic factor.

put the *MYC* gene under the control of the immunoglobulin enhancer sequences (5-8).

Proto-oncogene activation brings about their change into oncogenes; to date 50 to 60 oncogenes have been recognized (9). Although various proto-oncogenes have been identified in actuated, oncogenic form in human tumor genomes, the exact hereditary modifications that caused any of these actuations remain unclear. In a typical cell, proto-oncogene expression is controlled by its own transcriptional promoter – the sequence of DNA that controls the degree of transcription. Each proto-oncogene promoter enables the gene to react to an assortment of physiological signals. A proto-oncogene can be expressed at quite low levels depending on the cell's metabolic needs; nevertheless, on specific events, when necessary, the expression of the gene may be strongly induced (9).

The activation mechanisms of proto-oncogenes are as follows (5, 9):

Chromosomal translocation of a proto-oncogene from a location that cannot be transcribed to an adjacent location where it can be transcribed (*e.g.* the chromosomal translocation of the *MYC* oncogene in human Burkitt's lymphoma).

Point mutation of a proto-oncogene, where substitution of a single base by another base is translated by substituting an amino acid in the oncoprotein (*e.g.* a point mutation at codon 12 of the *RAS* oncogene).

Gene amplification, by incorporating multiple copies of an oncogene, resulting in increased production of oncoprotein (*e.g.* c-MYC in neuroblastoma).

Incorporation of a gene that promotes the transcription (promoter gene) near the proto-oncogene resulting in overexpression of the gene (*e.g.* the retrovirus carcinogenicity mechanism).

Example of the chromosomal translocation of the MYC oncogene and its signaling pathway. The three nuclear phosphoproteins N-MYC, C-MYC and L-MYC are highly related and constitute the so-called MYC family encoded by cellular proto-oncogenes. These proteins originate from genes located on chromosomes 2, 8 and 1, respectively. Constituent parts of MYC are the first exon non-encoding for protein and the protein-encoding third exon. The cell cycle is regulated through a nuclear DNA-binding protein that originates from the MYC gene. Transformation, dedifferentiation, immortalization and cell proliferation are promoted by the MYC gene family (10).

C-MYC transcription factor can be dimerized with MAX dimerization protein 1 (MAX), which is involved in the transcriptional regulation of target genes associated with

apoptosis and cell growth (11). The transactivation resulting from C-MYC deletions during nuclear translocation are involved in the negative regulation of adenomatous polyposis coli (*APC*) gene. This is regulated with the WNT pathway through β-catenin. Knockdown of APC can lead to carcinogenic expression of C-MYC. The activation of P53 or alternative reading frame (ARF) checkpoints are regulated by acute sustained oncogenic expression of C-MYC when C-MYC is deregulated (12).

MYC suppression is mediated by MYC–MAX with a regulation of the transcription of target genes using the ZBTB17 gene (*MIZ1*) line with the promoter Initiator element (Inr). Inr may be a MIZ1 cofactor or a silent C-MYC replacement of nuclear phosphoprotein (NPM) (13, 14).

The microRNA network may be also be regulated by C-MYC. This happens by suppressing dozens of miRs, such as *miR-17-92*. For example, lactate dehydrogenase expression is shown to be affected by *miR-34a* glutaminase expression, *miR-23a/b* and insulin signaling by *LET-7*. MicroRNAs include *miR-17* that targets phosphatase and tensin homolog gene (*PTEN*) and continuously induces protein kinase B (*AKT*). Additionally, it activates transcription factor E2F1 and pro-apoptotic recombinant human BCL2 apoptosis regulator (BCL2)-like protein 11 (BIML). Epithelial–mesenchymal transition and angiogenesis are associated with miRNAs downstream of C-MYC (10).

Relationship with tumor. Deregulation of C-MYC has been found in the majority of human tumors. Augmented C-MYC expression is the consequence of either dysregulation of the signal transduction pathway for its expression or by mutations in the C-MYC locus and C-MYC is the most commonly mutated gene in tumors. New therapeutic approaches to anticancer treatment target C-MYC since in many cases the cause of tumorigenesis is its overexpression. A second mutation that deactivates the apoptotic pathway (*e.g.* p53) is regulated by C-MYC oncogene when normal cell apoptotic pathways lack adequate survival factors. Apoptotic inhibition and cell survival are stimulated by two synergistic oncogenes, such as BCL2, BCL-xL, and RAS (10, 11).

Example of oncogene to proto-oncogene conversion after a point mutation. For human pancreatic cancer, the most common causative event is a single missense mutation that is acquired in transforming protein 21 gene (KRAS) that modifies the 12th codon leading ultimately to either valine or aspartate substitution for glycine, finally causing protein activation.

Pancreatic tumor progression and initiation involves activation of oncogenic KRAS by means of metastasis, metabolism alteration, resistance to drugs and alterations in signal transduction pathways (1). Astonishingly, in distal metastasis, advanced or precursor lesions of KRAS disappearance can lead to rapid regression of the tumor (15-17). This suggests that tumor initiation and maintenance, as well as progression are all affected by the presence of oncogenic KRAS (1).

There is a close correlation between NRAS, HRAS and KRAS A small membrane GTPase is encoded by KRAS in KRAS signaling. RAS is converted to an active form by the binding of GTP under the regulatory influence of Guanine exchange factors (GEFs). Conversely RAS is converted to its inactive form after hydrolysis of GTP to GDP, mediated by GTPase-activating proteins. Finally, a number of cellular processes, including cell proliferation are triggered by RAS proteins, through a number of different downstream signaling pathways. There is specific activity on different cell types for each member of the RAS family *via* gene regulation. KRAS is necessary for the development in addition to its donative effects on pancreatic colon and lung cancer, by causing the GTP to GDP hydrolysis after oncogenic mutations induce RAS activation. Different tumor types are associated with different regulation of KRAS (18).

The activated small membrane GTPase RAS is the cornerstone of the KRAS pancreatic signaling cascade, which in turn leads to the activation of the phosphoinositide 3-kinase (PI3K), rapidly accelerated fibrosarcoma (RAF)/methyl-ethyl-ketone (MEK)/extracellular signal-regulated kinases (ERK) and RAS-related protein B (RALA/B) signaling branches. There are many direct and indirect interactions among these branches, as well as several inhibitory and regulatory feedback loops.

Activation of a receptor-linked tyrosine kinase such as epidermal growth factor receptor may activate RAS in an upstream signaling cascade. In such cases, a phosphorylation cascade can be activated after homodimerization of epidermal growth factor receptors upon their binding to extracellular growth factors. This in turn leads to the activation of GEFs and growth factor receptor-bound 2 adaptor protein acting on RAS and allowing the substitution of GDP to GTP, ultimately leading to the formation of KRAS-GTP. RAF serine/threonine kinases are attracted toward the cellular membrane and activated by KRAS-GTP. RAS homolog enriched in brain (RHEB) is negatively regulated by a complex of proteins encoded by several genes, such as TSC complex subunit genes *TSC1* and *TSC2*, after transcription stimulation by ERK. PI3K containing p110 subunit (consisting of p110 and p85) is activated by KRAS-GTP, stimulating the PI3K signaling pathway which leads to the formation of phosphatidylinositol-4,5-tri-phosphate (PIP3) from phosphatidylinositol-4,5-bi-phosphate. Either mechanistic target of rapamycin kinase complex 2 (mTORC2) or phosphoinositide-dependent kinase-1 (PDK1) found on the plasma membrane can be activated by AKT after its stimulation by PIP3. PTEN, which acts as negative regulator of adenylate kinase 3 (AK3) is inhibited by the stimulation of nuclear factor kappa-light-chain-enhancer

of activated B-cells (NF-kB) under the influence of AKT. Additionally, mTORC1 bearsthe inhibitory TSC1/TSC2 complex that is blocked by AKT. Finally, the binding of GTP to the small RAL A/B GTPases cause its activation driven by the KRAS-GTP activation of RAL-GEF. TRAF family member-associated NFKB activator (TANK) inhibits the release of NF-kB when RALA/B binds TANK-binding kinase 1. In summary, protein translocation, proliferation and differentiation of cells are affected by the three signaling cascade branches (1).

It is now known that oncogenes can be formed or transferred to cells by means of viruses. Both DNA viruses and RNA retroviruses can transform the cells they infect (19, 20). DNA oncogenic viruses have as a common feature the interaction of their viral oncoproteins with specific regulatory proteins of the host cell, resulting in the onset of carcinogenicity. E7 protein encoded by human papilloma virus oncogenic types, adenovirus E1A protein, and SV40 virus large T-antigen all have the ability to bind to the peroxidase (pRB5) protein (19, 20). Retroviruses are oncogenic RNA viruses which can convert RNA into DNA by means of reverse transcriptase and then integrate into the DNA of the cell. Some retroviruses upon incorporation into the DNA of the cell 'capture' a proto-oncogene from the host and convert it to an oncogene, resulting in oncogenic transformation of the cell. Other retroviruses do not carry an oncogene but create tumors by their incorporation into the DNA at a location near a proto-oncogene, resulting in the activation of the proto-oncogene and its conversion to an oncogene (21). Several different oncogenes, derived from cell proto-oncogenes, have been identified by their homology with various transformed retroviral genes. Listed below are some examples of cellular oncogenes recognized by retroviruses: Simian sarcoma (SIS), McDonough feline sarcoma (FMS), erythroblastosis (ERBB), ABL, Harvey murine sarcoma (Ha-RAS), Kirsten murine sarcoma (K-RAS), avian sarcoma virus 17 (JUN), FBJ osteosarcoma (FOS), avian MC29 myelocytomatosis (MYC). Chemical carcinogens can also activate proto-oncogenes and are recognized as carcinogens with direct or indirect action. All chemical carcinogens have a common feature: the creation of electrophilic centers (22-24).

Tumor-suppressive Genes and Blockage of Carcinogenesis

In the normal cell, in addition to oncogenes, there are tumor-suppressive genes, which play a major role in the normal growth and differentiation of the cell and block the development of cancer. Tumor-suppressor genes form a huge group that exhibit one common characteristic: somehow, every single one of these genes protects the organism from neoplasia. Both copies of a tumor-suppressor gene must be in an inactive state before a cancer cell can proliferate or survive further. Lack or inactivation due to mutations of tumor-suppressor genes leads to cancer (1). Various tumor-suppressor genes are expected to lie spread around the genome of the humans and play a role in the advancement of various types of human neoplasia (25).

Examples of tumor-suppressor genes are retinoblastoma 1 protein (RB1) and *P53*. P53 protein, which is the product of the tumor-suppressor P53 gene, acts as a tetramer. Mutations of one allele in a cell can suppress the action of the P53 protein because all the tetramers will contain at least one mutant P53 protein. Mutations of the P53 tumor-suppressor gene are therefore prevalent. Retinoblastoma protein, on the other hand, acts as a monomer and hence its mutations are residual (4, 26).

Loss of heterozygosity may be caused by intermediate deficiencies, deletions of chromosomes, or abnormal mitotic divisions and is thought to reflect the loss of one or more tumor-suppressor genes (27).

Microsatellite DNA differs from the rest of DNA because its structure is based on the linear repetition of smaller subunits (up to six nucleotides) and does not code for proteins. Microsatellite DNA is used in genetic studies. The instability of microsatellite DNA reflects an increase in the rate of mutagenesis in microsatellite DNA sequences and thus in the entire genome and is associated with damage to the DNA-repair system (27).

The Clonal Theory of Oncogenesis

According to the clonal theory of oncogenesis, tumors start from a single cell. But the clonal origin of the tumors does not mean that a malignant tumor develops because of a single mutation. Oncogenes often act synergistically to cause malignant transformation. For example, we mention the synergistic effect of two oncogenes in transgenic mice, in which *RAS* and *MYC* oncogenes were transfected. *MYC* oncogene caused tumorigenesis only after 100 days and only in a small percentage of the transgenic mice. The *MYC* oncogene was initially discovered in the genome of an avian retrovirus and found to be activated through several alternative mechanisms in cancer cells: Proviral integration, gene amplification and chromosomal translocation. The *RAS* oncogene caused tumorigenesis earlier than the *MYC* oncogene, and after 150 days, 50% of the transgenic mice developed a tumor. In transgenic mice with both *RAS* and *MYC* oncogenes, cancer developed in 100% of the transgenic mice and in a much shorter period (28).

Programmed Cell Death (Apoptosis)

There are two forms of death of eukaryotic cells: Necrosis and apoptosis or programmed cell death. Necrosis is

caused by abrupt cellular damage (*e.g.* ischemia) or after physical or chemical injury. In necrosis, changes occur in the protoplasm resulting in increased cell volume, cell death and finally DNA decomposition by the release of lysosomal enzymes (4). However, apoptosis is a normal occurrence of normal tissue growth and changes occur in the nucleus (nuclear breakage). In apoptosis, DNA fragmentation due to an endogenous endonuclease precedes cell death and it appears that cell death in apoptosis is not a direct result of DNA fragmentation but of the cell's inability to repair extensive DNA damage. Since the most common form of cell death is apoptosis, it seems that inhibition of apoptosis is responsible for the development of cancer (29).

Several genes have been associated with apoptosis and either stimulate or inhibit it. For example, the proteins of the MYC and BAX proto-oncogenes, the *P53* tumor-suppressor gene and the E2F transcription factor activate apoptosis. On the contrary, the BCL2, ABL, and RAS oncoproteins inhibit apoptosis. Finally, RB may cause inhibition of the growth of human cancer cells (23, 29, 30).

Molecular Mechanisms of Angiogenesis in Solid Tumors

Angiogenesis and angiogenic factors. Angiogenesis is the development of new blood vessels (31). Angiogenesis naturally occurs during embryogenesis and healing of wounds, while occurring pathologically in rheumatoid arthritis, diabetic retinopathy, psoriasis, atherosclerosis and the development of solid tumors. The mechanism of angiogenesis as described in the literature involves the breakdown of the basement membrane, cell division and the migration of endothelial cells, and finally the anastomosis of the new vessel with a pre-existing one (32, 33).

Several angiogenic factors have been found that are expressed in solid tumors, such as platelet-derived endothelial cell growth factor, vascular endothelial growth factor, basic fibroblast growth factor and interleukin-8 (IL8). The activation mechanisms of angiogenic factors are under investigation, while hypoxia, and mutations in the *P53* and *IL8* have been found to be involved (34-37).

Natural inhibitors of angiogenesis. A large number of angiogenesis inhibitors are known and, in many cases, their genes have been isolated. The mechanisms of action of the natural inhibitors of angiogenesis to date are as follows (38, 39):

Inhibition of proteinases necessary for the basement membrane degradation of the blood vessels (*e.g.* plasminogen activator inhibitor and tissue inhibitor of metalloproteinase).

Inhibition of the action of growth factors on tumor vascular endothelial cells (*e.g.* α2 macroglobulin).

Induction of apoptosis of endothelial cells of tumors and metastases (*e.g.* tumor necrosis factor α, which is a cytokine, and angiostatin, which is a plasminogen fragment).

Conclusion

Oncogenes are the main genes contributing to the conversion of normal cells to cancer cells and tumor-suppressive genes block the development of cancer. The way they both act is complicated and needs further investigation to fully elucidate cancer pathways and carcinogenesis. In the modern era, there are specialized screening and laboratory methods that must be further developed through which mutations in cells can be avoided or blocked. Large studies and continuing research on oncogenes and tumor-suppressive genes may reveal important pathways in carcinogenesis in the future.

Conflicts of Interest

The Authors declare no potential conflicts of interest.

Authors' Contributions

Emmanuel N. Kontomanolis: Study conception and design, acquisition of data, drafting of article, analysis and interpretation of data, critical revision of article. Antonios Koutras: Drafting of article and analysis and interpretation of data. Athanasios Syllaios: Drafting of article and analysis and interpretation of data. Dimitrios Schizas: Drafting of article and analysis and interpretation of data. Aikaterini Mastoraki: Drafting of article and analysis and interpretation of data. Nikolaos Garmpis: Analysis and interpretation of data, drafting of article. Michail Diakosavvas: Analysis and interpretation of data, drafting of article. Kyveli Angelou: Analysis and interpretation of data, drafting of article. Georgios Tsatsaris: Analysis and interpretation of data, drafting of article. Athanasios Pagkalos: Analysis and interpretation of data, drafting of article. Thomas Ntounis: Analysis and interpretation of data, drafting of article. Zacharias Fasoulakis: Study conception, drafting of article and analysis and interpretation of data.

References

1 Nenclares P and Harrington KJ: The biology of cancer. Medicine *48(2)*: 67-72, 2020. DOI: 10.1016/j.mpmed.2019.11.001

2 Read RW: Metastasis. *In:* Intraocular Inflammation. Pavesio C, Ohno S, Orefice F and Rao N (eds.). Springer, Berlin, Heidelberg, pp. 1511-1514, 2016.

3 Derelanko MJ: Carcinogenesis. *In*: Handbook of Toxicology, Second Edition. Chapter 16, Derelanko MJ and Hollinger MA (ds.) CRC Press, Boca Raton, 2001.

4 Jan R and Chaudhry G-S: Understanding apoptosis and apoptotic pathways targeted cancer therapeutics. Adv Pharm Bull *9(2)*: 205-218, 2019. PMID: 31380246. DOI: 10.15171/apb.2019.024

5 Abel EL and DiGiovanni J: Multistage carcinogenesis. *In*: Chemical Carcinogenesis. Current Cancer Research. Penning T. (ed.) Humana Press, pp. 27-51, 2011.

6 Bataille P, Reynard A and Ducarme G: Spontaneous heterotopic triplets – A review of literature. J Gynecol Obstet Hum Reprod *46(8)*: 657-659, 2017. PMID: 28549987. DOI: 10.1016/j.jogoh. 2017.05.008

7 Kurebayashi J: Biological and clinical significance of HER2 overexpression in breast cancer. Breast Cancer *8(1)*: 45-51, 2001. PMID: 11180765. DOI: 10.1007/BF02967477

8 Klinakis A, Szabolcs M, Politi K, Kiaris H, Artavanis-Tsakonas S and Efstratiadis A: Myc is a Notch1 transcriptional target and a requisite for Notch1-induced mammary tumorigenesis in mice. Proc Natl Acad Sci *103(24)*: 9262-9267, 2006. PMID: 16751266. DOI: 10.1073/pnas.0603371103

9 Gariglio P: Oncogenes and tumor suppressor genes. *In:* Molecular Oncology Principles and Recent Advances. Camacho J (ed.). Bentham Science Publishing. pp. 64-82, 2012.

10 Hutter S, Bolin S, Weishaupt H and Swartling FJ: Modeling and targeting MYC genes in childhood brain tumors. Genes *8(4):* 107, 2017. PMID: 28333115. DOI: 10.3390/genes8040107

11 Ji X, Wang Y and Liu G: Expression analysis of MYC genes from *Tamarix hispida* in response to different abiotic stresses. Int J Mol Sci *13(2)*: 1300-1313, 2012. DOI: 10.3390/ijms13021300

12 Marandel L, Labbe C, Bobe J and Le Bail PY: Evolutionary history of c-myc in teleosts and characterization of the duplicated c-MYCA genes in goldfish embryos. Mol Reprod Dev *79(2)*: 85-96, 2012. PMID: 22213278. DOI: 10.1002/ mrd.22004

13 Wierstra I and Alves J: The c-myc promoter: still MysterY and challenge. Adv Cancer Res *99:* 113-333, 2008. PMID: 18037408. DOI: 10.1016/S0065-230X(07)99004-1

14 Dang CV: MYC on the path to cancer. Cell *149(1)*: 22-35, 2012. PMID: 22464321. DOI: 10.1016/j.cell.2012.03.003

15 Collins MA, Bednar F, Zhang Y, Brisset JC, Galbán S, Galbán CJ, Rakshit S, Flannagan KS, Adsay NV and Pasca di Magliano M: Oncogenic Kras is required for both the initiation and maintenance of pancreatic cancer in mice. J Clin Invest *122(2)*: 639-653, 2012. PMID: 22232209. DOI: 10.1172/JCI59227

16 Collins MA, Brisset JC, Zhang Y, Bednar F, Pierre J, Heist KA, Galbán CJ, Galbán S and di Magliano MP: Metastatic pancreatic cancer is dependent on oncogenic Kras in mice. PLoS One *7(12)*: e49707, 2012. PMID: 23226501. DOI: 10.1371/ journal.pone.0049707

17 Ying H, Kimmelman AC, Lyssiotis CA, Hua S, Chu GC, Fletcher-Sananikone E, Locasale JW, Son J and Zhang H: Oncogenic Kras maintains pancreatic tumors through regulation of anabolic glucose metabolism. Cell *149(3):* 656-670, 2012. PMID: 22541435. DOI: 10.1016/j.cell.2012.01.058

18 Koera K, Nakamura K, Nakao K, Miyoshi J, Toyoshima K, Hatta T, Otani H, Aiba A and Katsuki M: K-Ras is essential for the development of the mouse embryo. Oncogene *15(10)*: 1151-1159, 1997. DOI: 10.1038/sj.onc.1201284

19 Bosch FX and De Sanjosé S: The epidemiology of human papillomavirus infection and cervical cancer. Dis Markers *23(4)*: 213-227, 2007. PMID: 17627057. DOI: 10.1155/2007/914823

20 McLaughlin-Drubin ME and Munger K: Viruses associated with human cancer. Biochim Biophys Acta Mol Basis Dis *1782(3)*: 127-150, 2008. PMID: 18201576. DOI: 10.1016/j.bbadis. 2007.12.005

21 Aboulafia DM: Cancer screening in women living with HIV infection. Womens Health (Lond) *13(3)*: 68-79, 2017. PMID: 28952428. DOI: 10.1177/1745505717731970

22 Wang Y, Wang F, Sun T, Trostinskaia A, Wygle D, Puscheck E and Rappolee DA: Entire mitogen activated protein kinase (MAPK) pathway is present in preimplantation mouse embryos. Dev Dyn *231(1)*: 72-87, 2004. PMID: 15305288. DOI: 10.1002/dvdy.20114

23 Lohr JG, Stojanov P, Lawrence MS, Auclair D, Chapuy B, Sougnez C, Cruz-Gordillo P, Knoechel B, Asmann YW, Slager SL, Novak AJ, Dogan A, Ansell SM, Link BK, Zou L, Gould J, Saksena G, Stransky N, Rangel-Escareño C, Fernandez-Lopez JC, Hidalgo-Miranda A, Melendez-Zajgla J, Hernández-Lemus E, Schwarz-Cruz y Celis A, Imaz-Rosshandler I, Ojesina AI, Jung J, Pedamallu CS, Lander ES, Habermann TM, Cerhan JR, Shipp MA, Getz G and Golub TR: Discovery and prioritization of somatic mutations in diffuse large B-cell lymphoma (DLBCL) by whole-exome sequencing. Proc Natl Acad Sci USA *109(10)*: 3879-3884, 2012. PMID: 22343534. DOI: 10.1073/pnas.1121343109

24 Cancer Genome Atlas Network: Comprehensive molecular characterization of human colon and rectal cancer. Nature *487(7407)*: 330-337, 2012. PMID: 22810696. DOI: 10.1038/ nature11252

25 Chen JJL and Podlevsky JD: Telomeres and telomerase. Encycl Cell Biol *1:* 418-425, 2016. DOI: 10.1016/B978-0-12-394447-4.10042-2

26 Ayyanan A, Civenni G, Ciarloni L, Morel C, Mueller N, Lefort K, Mandinova A, Raffoul W, Fiche M, Dotto GP and Brisken C: Increased Wnt signaling triggers oncogenic conversion of human breast epithelial cells by a Notch-dependent mechanism. Proc Natl Acad Sci USA *103(10)*: 3799-3804, 2006. PMID: 16501043. DOI: 10.1073/pnas.0600065103

27 Liu Z, Turkoz A, Jackson EN, Corbo JC, Engelbach JA, Garbow JR, Piwnica-Worms DR and Kopan R: Notch1 loss of heterozygosity causes vascular tumors and lethal hemorrhage in mice. J Clin Invest *121(2)*: 800-808, 2011. PMID: 21266774. DOI: 10.1172/JCI43114

28 Soucek L, Whitfield JR, Sodir NM, Massó-Vallés D, Serrano E, Karnezis AN, Swigart LB and Evan GI: Inhibition of Myc family proteins eradicates KRas-driven lung cancer in mice. Genes Dev *27(5)*: 504-513, 2013. PMID: 23475959. DOI: 10.1101/gad.205542.112

29 Yang N and Sheridan AM: Cell cycle. *In*: Encyclopedia of Toxicology: Third Edition. Academic Press. pp. 753-758, 2014.

30 Bommer GT, Gerin I, Feng Y, Kaczorowski AJ, Kuick R and Love RE: p53-Mediated activation of *miRNA34* candidate tumor-suppressor genes. Curr Biol *17(15)*: 1298-1307, 2007. PMID: 17656095. DOI: 10.1016/j.cub.2007.06.068

31 Kontomanolis EN, Fasoulakis Z, Papamanolis V, Koliantzaki S, Dimopoulos G and Kambas NJ: The impact of microRNAs in breast cancer angiogenesis and progression. MicroRNA *8(2)*: 101-109, 2018. PMID: 30332982. DOI: 10.2174/2211536 607666181017122921

32 Wieland E, Rodriguez-Vita J, Liebler SS, Mogler C, Moll I and Herberich SE: Endothelial Notch1 activity facilitates metastasis. Cancer Cell *31(3)*: 355-367, 2017. PMID: 28238683. DOI: 10.1016/j.ccell.2017.01.007

33 Folkman J: Tumor angiogenesis factor. Cancer Res *34(8)*: 2109-2113, 1974. PMID: 4842257.

34 Dufraine J, Funahashi Y and Kitajewski J: Notch signaling regulates tumor angiogenesis by diverse mechanisms. Oncogene *27(38)*: 5132-5137, 2008. PMID: 18758482. DOI: 10.1038/ onc.2008.227

35 Bachelder RE, Wendt MA and Mercurio AM: Vascular endothelial growth factor promotes breast carcinoma invasion in an autocrine manner by regulating the chemokine receptor CXCR4. Cancer Res *62(24)*: 7203-7206, 2002. PMID: 12499259.

36 Rykala J, Przybylowska K, Majsterek I, Pasz-Walczak G, Sygut A, Dziki A and Kruk-Jeromin J: Angiogenesis markers quantification in breast cancer and their correlation with clinicopathological prognostic variables. Pathol Oncol Res *17(4)*: 809-817, 2011. PMID: 21560015. DOI: 10.1007/s12253-011-9387-6

37 Todorović-Raković N and Milovanović J: Interleukin-8 in breast cancer progression. J Interferon Cytokine Res *33(10)*: 563-570, 2013. PMID: 23697558. DOI: 10.1089/jir.2013.0023

38 Lan H, Lin F, Zhou Q, Huang L and Jin K: Strategies to improve drug distribution in solid tumor. Int J Clin Exp Med *9(2)*: 658-667, 2016.

39 Welti J, Loges S, Dimmeler S and Carmeliet P: Recent molecular discoveries in angiogenesis and antiangiogenic therapies in cancer. J Clin Invest *123(8)*: 3190-200, 2013. PMID: 23908119. DOI: 10.1172/JCI70212

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