

The Role of Oncogenes in Cancer Development

Nikolaos Andreas Chrysanthakopoulos*

Dental Surgeon (DDSc), Resident in Maxillofacial and Oral Surgery, 401 General Military Hospital of Athens, Athens, Greece Oncologist (MSc), Specialized in Clinical Oncology, Cytology and Histopathology, Dept. of Pathological Anatomy, Medical School, University of Athens, Athens, Greece

***Corresponding Author:** Nikolaos Andreas Chrysanthakopoulos, Dental Surgeon (DDSc), Resident in Maxillofacial and Oral Surgery, 401 General Military Hospital of Athens, Athens, Greece Oncologist (MSc), Specialized in Clinical Oncology, Cytology and Histopathology, Dept. of Pathological Anatomy, Medical School, University of Athens, Athens, Greece, **Email:** nikolaos_c@hotmail.com, nchrysant@med.uoa.gr

Abstract: Cancer is a genetic disease with undetermined etiology and its development and pro-gression characterized by special tumor cells, including sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing and activating invasion and metastasis. In this review we present the roles of some of the most important oncogenes that have an active role in cell signaling pathways and involved in cell surviving, proliferation and malignancy transformation. Several anti-malignant could target those cell signaling pathways, using monoclonal antibodies and special inhibitors in order to inhibit their effects in malignant transformation and development of cancer.

Keywords: Oncogenes, Signaling pathways, Mutations

1. INTRODUCTION

Cancer is a genetic disease, consists the 2nd most common cause of mortality after Cardiovascular Disease worldwide [1] and its development is the result of accumulation of genetic mutation in genes that implicated in cell proliferation control, cell differentiation and programmed cellular death or programmed cell death-apoptosis [2]. According to 'two-hit theory' no one genetic mutation alone is sufficient for cancer development, but several factors have to occur before its clinical appearance. Those factors play an essential role in cancer initiation and progression. The principal mechanisms that are responsible for cancer development involve damage of DNA repair pathways, normal gene (proto-oncogene) transformation into an oncogene, tumor suppressor gene mutation or genes mutations that involved in apoptosis process. Over the last decades significant progress has been made in regards to genes involvement in the mentioned processes [3]. The aim of the present review was to describe the role of the oncogenes in cancer initiation and progression.

2. ONCOGENES DETERMINATION

The first attempt for determining for the existence of oncogenes came from a study by

Steeling et al. which investigated retroviruses, a group of RNA viruses [4]. Those viruses consist of the following genes ENV, GAG and POL which are responsible for three different proteins, namely an envelope protein, a core protein and a reverse transcriptase, respectively. One of those viruses, the Rous sarcoma virus was found that caused malignancies in chickens and had another gene, the SRC gene which came from mammalian. That virus used its reverse transcriptase and had the ability to integrate reversibly into the mammalian genome and was able to make a DNA copy. The virus came out from the cell due to the process known as transduction and incorporated a mammalian gene as a segment of its genome. A new viral infection by the same virus had resulted in the expression of the mammalian gene which was oncogenic as the transduction process led to the production of an abnormal protein. That pathway has been associated with tumors development in animals, however in few cases is responsible as the cause of malignancies in humans, such as Human T-cell Leukemia Virus -1 (HTLV-1) [5]. Several methods were found to identify genes in human malignancies which are able to make transformations. A DNA infection for transformation was used by Shih et al. [6]. According to that procedure DNA was

extracted from a human tumor and a normal cell line was infected. That transformed cell could be identified as cells formed a monolayer in a cell culture and those cells were able to develop tumors in case injected into nude mice. Similar to retroviruses those trans-formed cells had an oncogene in their genome. In cases of human leukemias the analysis of chromosome translocations break points was a method to identify more oncogenes. Chronic Myeloid Leukemia (CML) is a clonal disorder, associated with the Philadelphia (Ph) chromosome and is characterized by the reciprocal translocation between the long arms of chromosomes 9 and 22[t(9; 22) (q34; q11)]. This activates the ABL oncogene by moving it from chromosome 9 and combining it with sequence located on chromosome 22[7]. In Burkitt's lymphoma at the breakpoint on chromosome 8 the MYC oncogene was identified and associated with the 8; 14 translocation (8; 14) (q24; q32) [8]. Approximately 200 different oncogenes have been identified as responsible for human tumors [9]. In normal cells the role of the proto-oncogenes which consist the non-transformed version of the oncogenes is essential for cell functions as they provide signals that lead to cell division or regulate programmed cell death and its activations is under control. Several factors are able to activate those and that situation can lead to abnormal expression and to cell transformation [10].

3. FUNCTIONS OF THE PROTO-ONCOGENES

As already mentioned the role of proto-oncogenes is essential for several cell functions as regulate important cell signaling pathways which include cell proliferation, adhesion, differentiation, cell cycle control and programmed cell death. The accumulation of genetic damage in the forms of activated proto-oncogenes can lead to cancer development. The RAS proto oncogenes are targets for many genotoxic carcinogens, and activation of the proto-oncogene may occur at various stages of the carcinogenic process.

Numerous proto-oncogenes can be activated in human tumors. Mechanisms that induce aberrant expressions of proto-oncogenes are gene amplification and chromosomal translocation or gene rearrangement. Amplification of proto oncogenes and possibly gene over expression during the absence of gene amplification occur in the development of many human tumors. Activation of proto-oncogenes by chromosomal translocation has been detected

at a high frequency in several hematopoietic tumors [10, 11].

4. GROWTH FACTORS

A growth factor (GF) usually it is a protein or a steroid hormone. Growth factors are important for regulating a variety of cellular processes, act as signaling molecules between cells and regulate cellular growth, proliferation, healing, and cellular differentiation. GFs bind to their own specific receptors or a group of receptors on the cell surface. Once bound to the receptors lead to the activation of intracellular signaling pathways. The final point of that activation is genes change expression which implicated in cell cycle regulation and cell differentiation [12]. They often promote cell differentiation and maturation, which varies between GFs. Epidermal GF (EGF) enhances osteogenic differentiation, whereas Fibroblast GFs and Vascular Endothelial GFs stimulate blood vessel differentiation (angiogenesis). Platelet and Derived GF (PDGF) is responsible for cell division, advancing the cell from the stationary phase G₀ into the G₁ phase of the cycle [13]. Insulin GFs (IGF-1 and IGF-2) are responsible for promoting G₁ cell cycle phase, functions that involved in normal cell growth and development, however are implicated in cancer development as well [14]. Another GF that is considered as a tumor promoter and suppressor is the Transforming GF β (TGF β). TGF β factor plays a role as inhibitor of epithelial, haematopoietic and stromal cell growth however acts as promoter of progression and invasion [15]. To be more specific at the early stages is able to inhibit cell proliferation and consequently suppresses tumor development. When the tumor develops it becomes resistant to TGF β cell proliferation inhibition and at later stages of cancer development, then malignant cells by secretion of TGF β factor promote tumor invasion and metastases.

4.1. Growth Factor Receptors

GF receptors consist proto-oncogenes or their functional homologues that receive signals from GFs and activate intracellular signaling pathways. The most important family of those GFs receptors which implicated in tumor development is the transmembrane protein receptor tyrosine kinase (RTK) family. Their structure consists of an extracellular domain to which the GF binds a transmembrane domain and one or two intracellular tyrosine kinase domains. At least 58 different transmembrane

receptor tyrosine kinases have been identified [16]. Once the GF binds to the receptor results in receptor's oligomerisation and receptor's tyrosine autophosphorylation. Those reactions lead to the activation of receptor's activity and donate phosphorylated residues which mediate the specific binding of cytoplasmic signaling proteins. The activated receptor transfers the signal from the inner membrane surface to the nucleus through various intracellular signaling pathways. These genes, when mutated, make up a large proportion of all known oncogenes. As these receptors are important in the development and progression of cancers they have become the focus of interest for the development of novel targets for anti-cancer therapy [17]. The ErbB family of contains four RTK, that are associated with the EGFR. In humans, the family includes the following transmembrane proteins, EGFR (ErbB-1), HER2/neu (ErbB-2), Her 3 (ErbB-3) and Her 4 (ErbB-4) that are receptors for EGF family members of extra cellular protein ligands. The EGFR family, interact with a wide range of downstream signaling pathways and implicated in cell growth, survival and differentiation [18]. In many malignancies, mutations that affect EGFR's activity or expression and lead to over-expression could lead in cancer development [19]. The mechanism of signal transduction by EGFR family have found out therapeutic targets as the interruption of EGFR signaling pathway, either by inhibiting intracellular tyrosine kinase activity or by blocking EGFR binding sites on the extracellular domain of the receptor can prevent the growth of EGFR-expressing tumors and improve the patient's survival. An antibody to HER2 receptor (herceptin) has been widely assessed for the breast cancer treatment [20]. PDGF-Rs are tyrosine kinase receptors cell surface for members of the PDGF family. The members PDGF-A and -B encoded by a different gene and regulate cell functions such as cell growth, development, cell proliferation, differentiation and many diseases including cancer. PDGF-receptors have been confirmed to be novel therapeutic targets and Imatinib, a tyrosine kinase inhibitor, has also been shown to inhibit PDGF-receptors [21,22]. The insulin-like growth factor 1 (IGF-1R) receptor is a transmembrane tyrosine kinase receptor that is activated by a hormone called insulin-like GF1 (IGF-1) and by a related hormone known as IGF-2. IGF-1 receptor mediates the effects of IGF-1, a polypeptide protein hormone which similar to insulin in molecular structure. Binding

of IGF-1 and 2 to their receptors (IGF-1R and 2R) mediates various effects in cancers which ultimately lead to increased translation of specific types of RNAs, whereas IGF-1 plays an important role in growth and continues to have anabolic effects in adults [23]. The Transforming GF beta (TGF β) receptors are a family of receptors and are implicated in TGF β cell signaling pathway. These receptors bind GF and cytokine signaling in the TGF- β family such as TGF β s (TGF β 1, TGF β 2, TGF β 3) growth differentiation factors (GDFs), myostatin, activin and inhibin, bone morphogenetic proteins (BMPs), anti-Müllerian hormone (AMH) and NODAL [24]. TGF β binds to TGF β -receptor 2 and this complex then rapidly lead to phosphorylation of TGF β -receptor 1 which in turn phosphorylates and activates members of the SMAD proteins which transduce signals from cytoplasm to nucleus [25]. One of the biological effects of TGF-beta is the inhibition of proliferation of most normal epithelial cells using an autocrine mechanism of action, and this suggests a tumor suppressor role for TGF-beta. Loss of autocrine TGF-beta activity and/or responsiveness to exogenous TGF-beta appears to provide some epithelial cells with a growth advantage leading to malignant progression. This suggests a pro-oncogenic role for TGF-beta in addition to its tumor suppressor role. During the early phase of epithelial tumorigenesis, TGF-beta inhibits primary tumor development and growth by inducing cell cycle arrest and apoptosis. In late stages of tumor progression when tumor cells become resistant to growth inhibition by TGF-beta due to inactivation of the TGF-beta signaling pathway or aberrant regulation of the cell cycle, the role of TGF-beta becomes one of tumor promotion [26].

5. SIGNALING PATHWAYS

Many of the receptors use common cell signaling pathways through which they transmit their signals to nucleus, however three essential pathways have been identified to play the main role in cancer development the RAS/mitogen activated protein kinase (MAPK) pathway, PI3-kinase (PI3-K)/AKT pathway, and the JAK/signal transducers and activators of transcription (STATs) pathway. The proteins that are implicated in those cell signaling pathways are members of the third group of proto-oncogenes, the signal transducers which are the cytoplasmic non-receptor protein tyrosine kinases and include 32 members. The phosphatidylinositol 3-kinase (PI3K) gene family is composed of the p110 catalytic subunit

and the p85 regulatory subunit. That family is implicated in proliferation, survival adhesion and motility [27]. The initial step in both the PI3-K and RAS mediated pathways, following GF binding, is autophosphorylation of the receptor and results in activation of the kinase function. The consequence of this is recruitment of a group of cytoplasmic signaling proteins with SH2 (src homology 2) and protein tyrosine binding domains. The first step of that signaling pathway is the receptor phosphorylation which is followed by the p85 subunit binding to the GF receptor that mediated by SH2 domain, which in turn activates the p110 subunit and leads to an increase in its activity and the final point is the phosphatidylinositol phosphates generation. AKT (protein kinase B) is another protein that is involved in that pathway and translocated to the plasma membrane where it is phosphorylated and activated by phosphoinositide-dependent kinase-1 (PDK-1). 13 substrates for AKT have been identified and are apoptosis regulators such as BAD, and cell growth and cell cycle regulators [27]. The final result of that cellular signaling pathway is the promotion of cell survival and resistance of apoptosis. A great amount of the GFs that are responsible for the PI3-K pathway activation, also activate the RAS/MAPK signaling pathway. The RAS gene family includes the HRAS, KRAS and NRAS onco-genes. The MAPK/ERK pathway, also known as the Ras-Raf-MEK-ERK pathway, is a group of cell proteins that transmits a signal from a receptor on the cell surface to the nuclear DNA. That signaling pathway includes various proteins, such as MAPK, mitogen-activated protein kinases, which is implicated by adding phosphate groups to a neighboring protein, which acts as an "on" or "off" switch. The signal starts when a signaling molecule binds to the cell surface receptor and ends when the nuclear DNA expresses a protein and makes some alterations in the cell, such as cell division. RAS proteins exist in equilibrium between GTP- and GDP-bound forms. In case one of the proteins in the pathway is mutated, it can become stuck in the "on" or "off" position, which is a necessary step in the development of many cancers. The nucleotide exchange factor SOS promotes the exchange of GDP for GTP to activate RAS [28, 29]. SOS, as a cytoplasmic protein must be translocated to the cell membrane, a process which is mediated by the adapter protein Grb2, and then activates RAS p21 protein. Interaction of inactive RAS with SOS protein leads to GDP/GTP exchange activates RAS. Another adaptor protein, Shc

following its phosphorylation by GFs is associated with the Grb2/SOS complex and lead to the same functional consequences as in case Grb2/SOS interacts directly with the receptor. GTPase activating proteins known as GAPs promote the hydrolysis of GTP to GDP and lead to RAS inactivation. Active RAS recruits the RAF, aserine/threonine kinase, to the plasma membrane and phosphorylates and activates its substrate MEK, Mitogen-activated protein kinase kinase, which then activates ERK kinase-Extracellular signal-regulated kinase, and the final result is the activation of transcription factors such as MYC and FOS or components of the cell cycle such as cyclin D1. RAS also activates the PI3-K pathway by binding to the catalytic sub-unit of PI3-K [30]. Janus protein tyrosine kinase (JAK) is a family of intracellular, non-RTK that transduce cytokine-mediated signals through the JAK-STAT pathway [31]. The JAKs possess two near-identical phosphate-transferring domains. The first domain exhibits the kinase activity, whereas the second negatively regulates the kinase activity of the first. Following ligand binding cytokine receptors are phosphorylated by JAKs. Those phosphorylated residues bind STATs through their SH2 domains and lead to STAT oligomerisation. The receptor release dimeric STATs that trans-locate to the nucleus and activate transcription. PI3-K signaling pathway also interacts with STATs and various GFs such as EGF and PDGF and is also able to activate the pathway following interaction with its own receptors. JAK/STAT signaling pathway abnormalities are mainly associated with the development of some leukemias and B cell malignancies. JAKs have seven defined regions of homology called Janus homology domains 1 to 7 (JH1-7). The JH3-JH4 domains of JAKs share homology with Src-homology-2 (SH2) domains. SRC is a non-receptor protein kinase which transduces signals and implicated in cellular functions such as proliferation, differentiation, motility and adhesion. The activated form of the SRC cytoplasmic tyrosine kinase consists an oncogene, however that tyrosine kinase preserved in its inactivated form by suppression of its activity through a specific tyrosine residue (Tyr530) phosphorylation in the protein carboxy terminus and through the interaction of that tyrosine residue with the Src-homology-2 domain. Another tyrosine residue (Tyr419) is essential in the regulation of SRC and its phosphorylation, consists a Src activity positive regulator. Dephosphorylation of the tyrosine residue Tyr530 by protein tyrosine

phosphatases or binding of ligands to receptor tyrosine kinases such as the PDGF Relieves the inhibitory restrictions on the kinase and leads to the activation of downstream signaling pathways such as PI3-K or RAS/MAPK[32]. In CML a chromosomal translocation leads to ABL onco-gene which is product is a cytoplasmic protein tyrosine kinase and has some characteristics in common with those of the SRC gene such as both SH2 and SH3 domains, a kinase domain and two C terminal domains -a domain through which it can bind to actin and a DNA binding domain. It has been observed that ABL gene is associated with DNA damage-induced apoptosis. In CML because of the chromosomal trans-location is produced the BCR-ABL fusion gene. The activation of the kinase activity of the BCR-ABL fusion protein is mediated by dimerisation of the protein through the BCR domain and leads to the BCR-ABL protein tyrosine residues phosphorylation. These residues then form special sites for adaptor molecules and other proteins which activate signal transduction pathways [7]. The RAS/MAPK pathway, PI3-K/AKT pathway and the JAK/signal transducers and activators of transcription (STATs) pathway are involved in BCR-ABL signaling [33].

6. NUCLEAR PROTO-ONCOGENES

A group of proto-oncogenes known as transcription factors implicated in gene expression control by binding of their products to determined locations of DNA and its role is to control transcription. The Myc family consists of three related human genes-c-myc, l-myc (MYCL), and nmyc(MYCN)and have been associated with human cancers. C-myc,also sometimes referred to as MYC, was the first gene to be discovered in this family, due to homology with the viral gene v-myc [34].MYC regulates cell proliferation and is implicated in cell differentiation and apoptosis[35] and is also able to drive cells that are in G0 phase into continuous cycling and can prevent cells from exiting the cell cycle[36]. Myc is activated by various mitogenic signals such as serum stimulation or by Wnt, Shh and EGF, through the MAPK/ERK pathway[37]. Myc activation results in numerous biological effects. The first to be discovered was its capability to drive cell proliferation (up regulates cyclins, down regulates p21), but it also plays a very important role in regulating cell growth(up regulates ribosomal RNA and proteins), apoptosis(downregulatesBcl-2), differentiation, and stem cell self-renewal. Nucleotide

metabolism genes are up regulated by Myc[38], which are necessary for Myc induced proliferation [39]or cell growth[40]. MYC family proteins and the other proteins in the extended network form a related subgroup within the much larger class of bHLHZ transcription factors [41]. In the case of MYC, homo-dimerization does not occur under physiological conditions, but a highly specific interaction with the small bHLHZ protein known as MAX results in stable heterodimer formation with specific DNA-binding activity [42].A major effect of c-myc is B cell proliferation, and gain of MYC has been associated with B cell malignancies and their increased aggressiveness, including histological transformation [43]. Myc proteins are transcription factors that activate expression of many pro-proliferative genes through binding enhancer box sequences (E-boxes) and recruiting histoneacetyl transferases (HATs) [44]. Many genes have been implicated as the target strands activated by MYC. Some, such as the cyclins and cyclin-dependent kinases, are involved in cell growth [45], whereas others, such as LDH-A, are involved in growth and metabolism. The more recent finding is the association of MYC with apoptosis and it is assumed that MYC affects transcription of genes in the apoptotic pathway. In addition, MYC has been identified as an inducer of telomerase activity [35]. The fos and jun proto-oncogenes are also transcription factors and belong to the AP-1 transcription family. Those factors dimerise and regulate transcription from promoters which contain AP-1 DNA binding sites that are located in genes associated with cellproliferation and differentiation. Their expression is induced transiently by a great variety of extracellular stimuli associated with mitogenesis and differentiation processes as mentioned. Activity of FOS and JUN is under strict control in the cell and they are regulated by phosphorylation of specific amino acids. Continuous over expression of fos or jun causes transformation of fibroblasts [46].

7. MECHANISMS OF ONCOGENE ACTIVATION

Under normal circumstances, expression of each of the proto-oncogenes is strictly controlled. Any abnormality of that control can lead to deregulation and the subsequent transformation of the cell. A number of pathways and procedures are responsible for proto-oncogenes activation and include protein over-expression, alteration in protein's structure and loss of normal control mechanisms. However, many

oncogenes can be activated by a number of mechanisms as does not exist only one mechanism of activation of any one oncogene. The activation of oncogenes involves genetic changes to cellular proto-oncogenes. The consequence of these genetic alterations is to confer a growth advantage to the cell. Three genetic mechanisms activate oncogenes in human neoplasms, mutation, gene amplification, and chromosome rearrangements. These mechanisms result in either an alteration of proto-oncogene structure or an increase in proto-oncogene expression. Because neoplasia is a multistep process, more than one of these mechanisms often contribute to the carcinogenesis by altering a number of cancer-associated genes. Full expression of the neoplastic phenotype, including the capacity for metastasis, usually involves a combination of proto-oncogene activation and tumor suppressor gene loss or inactivation [47].

7.1. Protein Structural Alteration

Protein structural alteration can be occurred in a number of different ways. A common gene that has been studied extensively is RAS and its point mutation. Point mutations, which are able to result in amino-acid substitutions, have been found at various locations in the gene, mainly at codons 12, 13 and 61. Those alterations have been seen in approximately 30% of human tumors. KRAS mutations have been found widely in colorectal, pancreatic and non-small-cell lung cancer. HRAS mutations are common in bladder and kidney tumors and NRAS mutations have been linked to hepatic cellular cancers and hematological malignancies [11]. Mutant RAS is locked in its activated state bound to GTP and consequently there is no need for growth factor stimulation and that situation induces ongoing signaling to the nucleus. Point mutations have also been found in the receptor protein tyrosine kinase genes such as MET in renal cancers and, especially, in the RET gene in Familial Medullary Thyroid cancers (FMTC) and Multiple Endocrine Neoplasia types 2A (MEN2A) and 2B (MEN2B). In FMTC and MEN2A, mutations in the extracellular domains at conserved cysteine residues are responsible for development of intermolecular disulphide bonds between RET molecules a situation that can lead to constitutive dimerization and activation, whereas in MEN2B, the common methionine to threonine mutation which is located at codon 918 can lead to increased protein kinase activity without the need for dimerization [16]. More

serious and larger structural alterations are the chromosomal translocations which are common in many lymphomas and leukemias. In CML has been observed the 9, 22 translocation which places the ABL oncogene on chromosome 9 next to the breakpoint cluster region (BCR) of the Philadelphia gene on chromosome 22. The fusion gene (ABL-BCR) which is produced in this process is responsible for a fusion protein with constitutive protein tyrosine kinase activity [7]. Truncation of a proto-oncogene can result in a shorter protein product and in constitutive activation. Deletion of the 3' end of the SRC gene leads to removal of part of the protein that binds to the SH2 domain which is required for maintenance of the inactive state [32].

7.2. Gene Amplification and Over-expression

Proto-oncogene amplification is responsible for over-expression of normal proteins and has been associated with malignant transformation. MYC gene amplification has been linked to a number of tumors. NMYC is amplified in late stage of neuroblastomas, whereas HER2 gene amplification is an important prognostic indicator in breast cancer [48]. In addition over-expression of EGFR showed that it was a strong prognostic indicator in head and neck cancer, ovarian, cervical, bladder and oesophageal cancers [49].

7.3. De-Regulated Expression

That mechanism of activation is obvious in MYC oncogene which exists in Burkitt's lymphomas. MYC's expression is normally under control. In Burkitt's lymphoma the MYC gene is translocated to one of the immunoglobulin loci in the majority of Burkitt's lymphoma patients. The translocation between chromosomes 8 and 14 involving MYC and the immunoglobulin heavy chain gene is seen in approximately 80% of cases of Burkitt's lymphoma [50]. In the remaining 20% of cases the translocation implicates either the κ light chain gene on chromosome 2 or the λ light chain gene on chromosome 22. Breakpoints can be found either in the first intron or exon 1 of MYC, immediately 5' to the MYC gene or distant to the gene by up to 100 kb. In all cases MYC coding exons 2 and 3 of, are intact. The effect of that translocation is responsible for the deregulation of MYC gene expression probably involving regulatory fragments from the immunoglobulin loci and results in over-expression of the MYC gene with continuous signaling and consequent cell proliferation. MYC is also implicated in other hematological

malignancies. In multiple myeloma translocation of MYC also has been found into one of the immunoglobulin loci however in this disease, unlike in Burkitt's lymphoma, the translocation is a secondary characteristic. In some cases of T-cell ALL, the MYC gene is translocated into one of the T-cell receptor loci [51, 52].

8. CONCLUSION

The dominant reason for the research in regards to oncogenes is to identify them as possible diagnostic and prognostic indicators in cancers and as possible novel therapeutic targets. However, it must be highlighted that tumors are not the result of a mutation in a single gene but they are the end-point of a pathway of gene activation which implicates the oncogenes but also other important genes such as the tumor suppressor genes and genes involved in cell cycle control, in addition to epigenetic phenomena such as DNA methylation and histone modifications.

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