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Review Article

Molecular Biology of Oncogenes in Carcinogenesis: An Essential Review

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Abstract

Cancer is a genetic disease with unclear etiology, whereas its appearance and progression is characterized by special events such as sustaining proliferative signaling, evading growth suppressors, enabling replicative immortality, resisting cell death, inducing and activating invasion and metastasis. The disease arises from mutations in genes, oncogenes and tumor suppressor genes, that are implicated in growth, differentiation, or death. An oncogene is a mutated gene whose its protein is produced in higher quantities or whose altered product has increased activity and therefore acts in a dominant manner. In tumor suppressor genes the mutation has caused a loss of function, and therefore most are recessive in nature because both alleles must be mutated, as a mutation in only one allele is sufficient for an effect. More than 100 oncogenes and at least 15 tumor suppressor genes have been identified. In the current review we focus on the roles of some of the most important oncogenes that have an active contribution in cell signaling pathways and implicated in cell surviving, proliferation and malignancy transformation. Those cell signaling pathways are the target of diverse anti-malignant drugs, such as special inhibitors and mono-clonical antibodies in order to inhibit their effects in malignant transformation and development of cancer.

Keywords: Oncogenes, Signaling Pathways, Mutations, Carcinogenesis

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Introduction

Cancer is a genetic disease, and the 2nd most common cause of mortality worldwide after Cardiovascular Disease [1] and is linked with genetic mutation accumulation in genes involved in cell proliferation control, differentiation and 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, as it seems to play an essential role in cancer initiation and progression. The main mechanisms that are responsible for cancer development concern DNA repair pathways damage, normal gene (proto-oncogene) transformation into an oncogene, tumor suppressor gene mutation or genes mutations which are implicated in apoptosis process. Over the last decades significant progress has been made regarding the genes involvement in the mentioned processes [3].

Studies on retroviruses have resulted in great insights into cancer biology and have become the foundation of our knowledge of oncogenes. Stehelin et al. investigated retroviruses, a group of RNA viruses and that was the first attempt for determining the existence of oncogenes [4]. Several landmark experiments were performed based on the initial observation that viruses could cause cancer

in animals, and the results pointed to the discovery of oncogenes. Those viruses carry the following genes *gag*, *env* and *pol* which are responsible for three different proteins, namely a core protein, an envelope protein, and a reverse transcriptase, respectively. One of those viruses, the Rous sarcoma virus (*Rsv*) was responsible for malignancies in chickens and had another gene, the *src* gene which came from mammalian, and it was the first so-called "oncogene", known as *v-src* [5]. It has been also reported that there was a gene with an homologous sequence to *v-src* in uninfected chickens. Moreover, upon further investigation, this gene could be found in diverse organisms and humans. Therefore, a fundamental principle of cancer biology was revealed, almost all known oncogenes were altered forms of normal genes or proto-oncogenes [4]. The name proto-oncogene is used in cancer biology to distinguish the normal cel-lular (*c*) gene, eg. *c-src*, from the altered form transduced by retroviruses (*v*), eg. *v-src*. The *v-src* sequence lacks the carboxy-terminal negative regulatory domain present in *c-src* which has point mutations throughout the gene[6].

The retroviruses life cycle characterizes them as intracellular parasites as they rely on their host cell for energy supply and for producing viral proteins. After injecting their infectious nucleic acid (RNA) into a host cell, the viral RNA is first reverse-transcribed into DNA and it is known as a pro-virus. This is an exception to the central dogma of genetic information unidirectional flow: DNA→RNA→protein. This provirus DNA is integrated randomly into the host chromosome where it will be replicated, transcribed, and translated as host DNA. The viral DNA translation then produces viral proteins for the new viral particles synthesis. During evolution, the virus is able to acquire genes fragments from the host integration regions, and this process may lead to carcinogenesis [7]. The *Rsv* acquired a truncated form of *c-src*. Similarly, *Rsv* using its reverse transcriptase is able to integrate reversibly into the mammalian genome and to make a DNA copy. With the procedure of transduction the *Rsv* exited the cell and integrated a mammalian gene as a segment of its genome [8,9]. Alternatively, and depending on the integration site, viral DNA may be translated as a fusion protein, in connection with cellular DNA, leading to a novel fusion protein, or host genes may fall under the viral regulator sequences regulation. The resulting disruptions to host gene expression are other mechanisms of virus-induced oncogenesis[9]. The mentioned findings could be useful for understanding the carcinogenesis mechanisms because although viruses are not the major cause of human cancers, the mechanism of proto-oncogenes oncogenic activation is similar. For instance, chromosomal translocations may have the same consequence as the integration into a host chromosome of a virus. A crucial gene may come under the influence of novel regulatory sequences and may result in abnormal gene product quantities. The new gene configuration may act as an oncogene [9,10]. A new *Rsv* infection can lead to the mammalian gene expression which was oncogenic as the transduction process resulted in abnormal protein production . That pathway has been linked with tumors development in animals, however in a limited number of cases is responsible for human malignancies development, such as Human T-cell Leukemia Virus -1 (HTLV-1) [11].

Several methods were detected to identify genes in human malignancies which are able to make transformations. Shih et al. used a DNA infection for transformation as DNA was extracted from a human tumor and a normal cell line was infected. That transformed cell was visible as cells formed a monolayer in a cell culture and those cells could develop tumors in case injected into nude mice. Similar to retroviruses those transformed cells carried an oncogene in their genome [12].

In human leukemias the chromosome translocations break points analysis was a method to identify more oncogenes. Similarly, in Burkitt's Lymphoma (BL) at the breakpoint on chromosome 8 the *myc* oncogene was identified and associated with the 8;14 translocation t (8; 14) (q24; q32) [13]. In Chronic Myeloid Leukemia (CML), which is associated with the Philadelphia (Ph) chromosome a reciprocal translocation between the long arms of chromosomes 9 and 22 [t (9; 22) (q34; q11)] was detected. That translocation activates the *abl* oncogene by moving it from chromosome 9 and combining it with sequence located on chromosome 22 [14].

Approximately, more than 100 dominant oncogenes have been identified as responsible for human tumors[15]. Proto-oncogenes role in normal cells, which consist the nontransformed version of the oncogenes, is essential for cell functions as they take part in signaling pathways that result in cell division or regulate programmed cell death and their activations is under control. Several factors are able to activate those and that activation can result in abnormal expression and cell transformation [16].

The aim of the present review was to focus on the molecular biology and the roles of some of the most important oncogenes that have an active contribution in the process of carcinogenesis.

Oncogenes Functional Classes

Oncogenes and their normal cellular counterparts, the proto-oncogenes, can be classified by their function into diverse classes (Table 1) [17]. A number of those genes encode growth factors, e.g., *sis* (PDGF B-chain), *hst* (FGF-like factor), etc., which are able to stimulate tumor cell proliferation by autocrine or paracrine mechanisms, but by themselves may not be sufficient to sustain the transformed phenotype. Another type of oncogene codes for altered growth factor receptors,many of which are associated tyrosine kinase (TK) activity. Those include the *erb B* (EGF receptor), *src* family of oncogenes, and *fms* (CSF-1

receptor). For some of those receptor-like, TK-associated membrane proteins, the actual ligand is unknown, e.g. *met*, *ros*, and *trk* [18]. A 3rd oncogene products class is membrane-associated, guanine nucleotide-binding proteins such as the Ras proteins family. These proteins bind GTP, have associated GTPases, and act as signal transducers for cell surface growth factor receptors. The transforming *ras* oncogenes have been mutated in such a way as to render them constitutively active by maintaining them in a GTP binding state, most possible because of a defect in the associated GTPase activity[19]. A 4th receptor class that has not associated TK activity is the *a1b* adrenergic receptor and the *mas* gene product (angiotensin receptor) [18]. A 5th class is the cytoplasmic onco-proteins with serine/threonine protein kinase activity. Those concern the products of the *mos*, *raf*, *pim-1*, and *cot* genes. An important member of that class is the c-Raf protein, activated by a variety of TK-associated rece-ptors. It is evident that *c-raf* acts as an intermediate member in the signaling pathway between *ras* and the cell nucleus by activating the Mitogen Activated Protein (MAP) kinase cascade. The *raf* oncogenic form has lost part of its regulatory amino-terminal sequence and seems to be constitutively active. C-crk is also a cytoplasmic protein, and it appears to act by stabilizing TKs associated with the Src onco-proteins family [20]. A 6th class is cytoplasmic regulators like *crk*, which influence phospho-tyrosine-containing proteins. The last class, a large class of oncogenes code for nuclear transcription factors such as *jun*, *fos*, *myb*, *myc*, *erb A*, and *rel* [21,22] (Table 1).

For some of those, the oncogenic alteration that makes them transforming onco-proteins is a mutation that results in loss of negative regulatory components (e.g., for *fos*, *jun*, and *myb*), and in other cases (e.g. *erb-A* and *rel*) the activating mutations lead to the active domains loss, producing a mutant protein that prevents the normal gene product activity, known as a dominant-negative mutation. Mutations of the tumor suppressor gene *p53*, in sort of a ‘‘reverse twist,’’ produce a dominant-negative effect by producing a protein that in this case prevents the action of a tumor suppressor function [22, 23].

Table 1. *Oncogenes Functional Classes [17]*

Class 1	**Growth Factors**	**Class 2**	**Receptor and non Receptor protein-TK**	**Class 3**	**Membrane Associated G- proteins**
sis	PDGF B-chain GF	*src*	Membrane-associated non receptor protein TK(M-ANRP-TK)	*K-ras*	Membrane associated GTP-binding/GTPase
int-1	GF (?)	*erbB*	Truncated EGFR protein TK	*H-ras*	Membrane associated GTP-binding/GTPase
int-2	FGF-related GF	*neu*	Receptor-like protein-TK	*N-ras*	Membrane associated GTP binding/GTPase
FGF-5	FGF-related GF	*abl/bcr-abl*	Non receptor protein-TK	*gip*	Mutant activated form of G_i α
hst (*KS3*)	FGF-related GF	*ret*	Truncated receptor-like protein-TK	*gsp*	Mutant activated form of G_s α
Class 4	**Receptors lacking protein kinase activity**	*lck*	M-ANRP-TK	**Class 7**	**Nuclear transcription factors**
A1β	Angiotensin receptor	*fgr*	M-ANRP-TK	*myb,myc*	Sequence-specific DNA -binding protein
mas	Angiotensin receptor	*yes*	M-ANRP-TK	*N,L-myc* *lyl-1,ets* *jun*	Sequence-specific DNA -binding protein S-sDNA-bp;part of AP-1
Class 5	**Cytoplasmic protein-Serine Kinases**	*met*	Soluble truncated receptor-like protein-TK (STR-LP-TK)	*evi-1,ski,* *av,Hex2.4*	Transcription factor *maf,gli-1, v* Transcription fact (?)
mos	Cytoplasmic protein-serine kinase (cytostatic factor)	*trk*	STR-LP-TK	*erbA*	Dominant negative mutant T3 receptor
cot	Cytoplasmic protein-serine kinase (?)	*kit*(*W locus*)	Truncated stem-cell receptor protein-TK	*rel*	Dominant negative mutant NF-κB-related protein
pim-1	Cytoplasmic protein-serine kinase	*fms*	Mutant CSF-1 receptor protein-TK	*fos*	Combines with c-jun to form AP-1 transcription factor
raf/mil	Cytoplasmic protein-serine kinase	*ros*	Membrane-associated receptor-like protein-TK	*p53*	Mutant form may sequester wild-type p53 growth suppressor

Class 6 Cytoplasmic regulators	*fps/fes* Non receptor protein-TK	*pbx* Chimeric E2A-homeobox transcription factor
crk SH-2/3 protein which bind to (and regulates?) phospho-tyrosine-containing proteins	*sea* Membrane-associated truncated receptor-like protein-TK	**Other** *dbl* Cytoplasmic truncated cyto skeletal protein (?) *bcl-2* Inhibits programmed cell death (apoptosis)

Oncogenes Cell Transforming Ability

Proto-onc genes are normal cellular genes that are related to the retroviruses transforming (*onc*) genes. Because of the mentioned association it is thought that those genes are potential cancer genes. In some tumor types, *proto-onc* genes are expressed more than in normal cells or are mutated. Under those circumstances, *proto-onc* genes are suggested to be active cancer genes according to the following ways. The first hypothesis suggests that one activated *proto-onc* gene is sufficient to cause cancer. The second hypothesis suggests that an activated *proto-onc* gene is a necessary but not a sufficient cause of cancer. However, transcriptionally activated or mutated *proto-onc* genes are not consistently associated with the tumors in which they are occasionally found and are not able to transform primary cells. Moreover, no one activated *proto-onc* gene and a complementary cancer gene with transforming ability has been isolated from a malignant tumor. Therefore, there is still no evidence that activated *proto-onc* genes are sufficient or even necessary to cause cancer [24,25].

As mentioned the gene transfer procedure, known as DNA transfection, has been implicated as a process for detecting oncogenes. Based on experiments, it has been recorded that DNA segments from a diversity of animal and human tumors are responsible for transformation of cultured NIH-3T3 mouse fibroblasts [26-28]. Those transforming DNA segments carry sequences homologous to known *v-onc* genes, based on the use of probes developed to the retroviruses oncogenes. The mentioned observation led to the concept that cellular *onc* genes activation can occur either by recombination with retroviral genomes, or by some sort of somatic mutational event leading to cellular *proto-onc* genes activation or aberrant expression. Evidence based on experimental research showed that point mutations, gene amplification, and chromosomal translocations can lead to cellular *proto-onc* genes activation or increased transcription [10,29].

The first attempt to reveal transforming or ‘‘cancer’’ genes in the cellular DNA of malignantly transformed cultured cells and tumors, reported by Avery et al. [30]. The authors showed that DNA isolated from a virulent strain of *pneumococci* could transform a non-virulent strain into a virulent one with the cellular markers. Moreover, the experiments by Hill and Hillova [31] recorded that DNA from Rsv-infected cells could transform cells as well as produce complete Rsv.The mentioned observations led to the concept that DNAfrom cells transformed by chemical carcinogens or DNA from malignant cells themselves might be able to transform normal cells into malignant ones.

Shih et al. reported the first evidence, that DNA from cells transformed with chemical carcino-gens could transform other cells, as showed that DNA from 3-methylcholanthrene (3-MC)-transformed mouse fibroblasts could morphologically transform a line of ‘‘normal’’ 3T3 mouse fibroblasts known as the NIH/3T3 line, [32] which has become the gold pattern for testing for transforming DNA. Those experiment procedures transfer intact DNA into whole cells, and the transformed cells were visible because the original transformers proliferated to form transformed cells colonies or foci that accumulated on one another instead of growing as flat monolayers of cells as occurs to normal fibroblasts [33]. In case of using DNA from non transformed NIH/3T3 cells in the transfection assay, the recipient cells were not morphologically transformed, and consequently were not tumorigenic. It is obvious that the ‘‘normal’’ fibroblasts treatment with the chemical carcinogen 3-MC in some way changes the cells’ DNA so that it carries the genetic information to induce a malignant phenotype in cells into which it is transfected [33]. Laboratory experiments confirmed those observations, thus adding chemical carcinogen-alteration of DNA to retroviral DNA as a means to induce malignant transformation, after integration into a cell’s genome. Other chemically activated transforming DNAs concern those extracted from ethylnitrosourea-induced rat neuroblastomas, benzo(a) pyrene (BP)-induced rabbit bladder carcinoma [12] 7,12-dimethyl-benz (a) anthracene [benzanthracene (DMBA)-induced mouse bladder carcinomas, and N-methyl-N0-nitro-N-nitrosoguanidine (MNNG)-transformed human cells [34,35].

DNA sequence analysis of the isolated transforming DNA sequences has been confirmed, and it appears that the same transforming genes are activated in neoplasms of the same differentiated cell type, regardless of the origin of the neoplasm virally or chemically induced or occurred spontaneously. Regarding the identity of those transforming genes and whether they corresponded to any known *proto-onc* gene or retroviral *onc* genes, was observed that based on the probes developed to the

c-onc and *v-onc* genes, the experiment to research their sequence homology against the cloned transforming genes isolated from various neoplasms and transformed cell lines was uncomplicated. Initially, probes developed to the *v-onc* sequences *src*, *myc*,*ras*, *erb*, *fes*,*myb,mos*, and *sis* were used to test sequence homology to the isolated transforming sequences by nucleic acid hybridization [27].

Experiments showed that the human lung and bladder carcinoma transforming genes detected by DNA transfection in the NIH/3T3 transformation assay were homologous to the *ras* genes of *v-K-ras* and *v-H-ras*, respectively [36]. Other human carcinomas and human tumor cell lines also carry the *K-ras* gene, including carcinomas of the lung, pancreas, colon, gallbladder, urinary bladder, and rhabdomyosarcoma [37]. Moreover, a third ras-like gene was discovered in the transforming sequences from a human neuroblastoma weakly homologous to both *v-H-ras* and *v-K-ras*. This transforming gene represents a 3rd member of *ras* gene family and has been defined *N-ras* [38]. The involvement of different *ras* genes in different types of human cancers suggests that *ras* gene family members may be involved in some general way in regulating the phenotypic characteristics of a diversity of human malignant tumors. However, the cellular *ras* genes activation in human cancers gives the first direct association between the retroviruses transforming genes and human cancer [39].

Similar experiments have indicated that human cancer-transforming genes are induced by the activation of cellular *proto-onc* genes. To be more specific, hybridization analysis of restriction endonuclease–digested cellular DNAs from lung carcinomas, human bladder and normal human cells with cloned probes of v-H-ras and v-K-ras sequences and with cloned probes of the biologically active transforming gene from human bladder cancer has shown that the activated tranforming genes of lung and bladder carcinomas are homologous to the *ras proto onc* genes of normal cells [40]. In addition, when viral transcriptional promoter LTR sequences from murine or feline retro-viruses are associated with the *ras proto-onc* gene isolated from normal human cells, oncogenic transformation of NIH/3T3 mouse fibroblasts is visible and an increased expression of the *p21* gene product of the *proto-onc ras* gene was revealed in the transformed cells an observationsuggesting that increased expression of a ‘‘normal’’ *proto-onc* gene is able to induce oncogenic transformation [41]. However, it is also possible to activate *proto-onc* (*c-onc*) genes through other mechanisms, such as gene amplification and somatic mutation.

C-onc genes activation is attributed to mechanisms that are responsible for genes activation during cell transformation or tissue differentiation, and concern point mutations, gene amplification, gene rearrangement, and increased transcription due to alterations in chromatin packaging.

Moreover, retrovirus enhancer regions (LTRs) insertion next to *c-onc* genes or mutation in *c-onc*gene coding sequences is able to alter their function. Some of these mechanisms have been identified *in vitro* or animal experiments, but all could potentially be implicated in *c-onc* gene activation during carcinogenesis in humans. Proto-oncogenes are present in all human and animal cells and they obviously must be activated by some endogenous, such as faulty repair of oxidative damage from normal cellular processes or exogenous agents, such as chemical carcinogens, ultraviolet light, to trigger the cancer process. Many genetic lesions have been detected in human tumors and are possible parts of the carcinogenic process [42].

DNA-RNA hybridization using *v-onc* gene cDNA probes has resulted in the examination of a wide diversity of human tumors for expression of cellular *c-onc* genes [43]. Expression of genes, (transcription into RNA), homologous to *v-onc* genes in human tumors is present in lymphomas, leukemias, carcinomas, neuroblastoma, various sarcomas, choriocarcinoma, and teratocarcinoma [44].

The DNA transfection experiments proposed that transforming ability is a dominant characteristic. More particularly, if a transforming *onc* gene is activated in or transfected into a normal cell, it arrests the cell’s genetic mechanism and turns it into a malignant cell. This option is may be wrong as the NIH/3T3 cell is a cancer cell. Indeed, ‘‘untransformed’’ NIH/3T3 cell cultures subpopulations are tumorigenic and metastatic under the right circumstances [45] although transformation with a *ras* gene appreciably increases the malignant potential of these cells. Moreover, transfection with at least two *onc* genes is necessary to transform normal diploid fibroblasts in culture, supporting the concept that malignant transformation is a multistage process. Finally, cell hybridization between malignant and normal cells indicates that the hybrid cells formed are more likely to be tumorigenic [46]. Consequently, the complete malignant phenotype expression is not possible to be attributed to insertion or activation of a single ‘‘cancer gene,’’ and in most cases appears to implicate tumor suppressor genes loss.

Oncogene Activation and Carcinogenesis

Oncogene activation is caused by chromosomal rearrangements, mutations, and gene amplification and leads to a growth advantage or increased survival of cells with such alterations. The mentioned mechanisms are responsible for an alteration in the oncogene structure or an increase or deregulation of its expression [47]

Chromosome translocations and inversions are classical cytogenetic abnormalities in cancer cells. In solid tumors and hematopoietic malignancies, the translocations and inversions deregulate or increase the oncogene transcription. In cancer such as prostate, gene fusion occurs between a gene that carries a promoter which is

very active in the target cells, and another that shows the oncogenic activity (e.g.,ERG1)[48]. In hematopoietic malignancies of T- and B- cells, the most common activation mechanism is similar to *myc* deregulation, whereas in soft-tissue sarcomas and myeloid cancers, gene fusion is more common [49].

In case an oncogene is activated by mutation, the encoded protein structure is changed in a way that enhances its transforming activity. Oncogenes are characterized by many types of mutations [50].For instance, the *ras* oncogenes (*K-ras,H-ras,N-ras*),which encode proteins with guanosine nucleotide-binding activity and intrinsic guanosine triphosphatase activity. Mutations in codon 12, 13, or 61, leads the *ras* genes to encode a protein that remains in the active state and continuously transduces signals by linking TKs to downstream serine and threonine kinases [51]. Those continuous signals induce incessant cell development. Moreover, *ras* family oncogene mutations have been associated with exposure to environmental carcinogens. *K-ras* mutations are detected in carcinomas of the lung, colon, and pancreas, whereas *N-ras* mutations occur mainly in Acute Myeloid Leukemia (AML) and the Myelodysplastic syndrome [52].

Braf gene activating point mutations occur in 59% of melanomas, 18% of colorectal cancers, 14% of hepatocellular carcinomas, and 11% of gliomas [53]. Most of the Braf mutations change the valine residue at position 599 to glutamic acid (V599E), an alteration that occurs within the Braf protein kinase domain, leading to a constitutively active protein that uncontrollably stimulates the MAP kinase cascade, thereby deregulating genes implicated in cell survival, proliferation, and differentiation [53,54]. In melanoma cases, Braf mutations can precede neoplastic transformation, as several types of nevi have BRAF mutations [53].

A gene amplification , which usually occurs during tumor progression, is the dihydrofolate reductase gene (DHFR)amplification in methotrexate-resistant Acute Lymphoblastic Leukemia(ALL) [55]. DHFR amplification is accompanied by cytogenetic alterations that reflect amplification of oncogenes [56,57]. The amplified DNA segment usually contains several hundred Kbs and many genes.

Four different oncogene family members are often amplified, *ras*, *myc*, *cyclin D1* (or *CCND1*), and EGFR. *myc* is amplified in breast cancer, SCLC, esophageal, cervical, ovarian and head and neck cancer, whereas *N-myc* amplification associates with an advanced tumor stage [58].

The t(11;14) translocation contrasts *cyclin D1* and immunoglobulin enhancer components and is characteristic of mantle-cell lymphoma [59].*Cyclin D1* amplification is also found in esophageal,breast, hepatocellular, and head and neck cancer. *EGFR* (*ERBB1*) is amplified in head and neck cancer and glioblastoma cases. *ERBB2*, also known as *Her 2/neu*, amplification of in breast cancer associates with a poor prognosis [60].

The association of the most common oncogens with carcinogenesis is presented in Table 2.

Table 2. *The association of the most common oncogens with carcinogenesis*

Oncogens	**Associated Cancers**
ras	Breast, lung, colon, pancreas, liver, skin, thyroid, bladder, kidney, seminoma, melanoma, leukemia (some types) [61]
myc	Colon, lung (squamous, adenocarcinoma, SCL), hepatocellular, cutaneous, bladder, prostate, breast, oesophagus, gastric, pancreatic, neuroblastoma, ovarian, uterine, endometrial, acute myeloid leukemia, diffuse large B cell lymphoma [62]
bcr/abl	Chronic myeloid leukemia, certain variants of acute lymphoblastic leukemia, acute myeloid leukemia, AML-not otherwise specified [63]
bcl-2	Follicular lymphoma, diffuse large-cell lymphomas, B-cell chronic lymphocytic leukemia, gastric, breast, prostate, hepatocellular, lung (NSCLC)[64]
Nf-kB	Colon, breast, cervical, ovarian, vulvar, uterine (endometrial) prostate, testicular, penile, kidney, bladder, lung, mesothelioma, esophageal, laryngeal, liver, pancreatic, stomach, thyroid, parathyroid, melanoma, squamous cell carcinoma, head and neck, cylindromatosis, GIST, trichoepithelioma, hilar cholangiocarcinoma, oral carcinoma, tongue, astrocytoma, Hodgkin lymphoma, acute lymphoblastic leukemia, acute myeloid leukemia, acute T cell leukemia, acute nonlymphocytic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, Burkitt lymphoma (EBV), Mantle cell lymphoma, myelo-dysplastic syndrome, multiple myeloma, diffuse large B cell lymphoma, MALT lymphoma, marginal zone lymphoma, Waldenstrom's macroglobulinemia [65]
erbB-2 (HER-2/neu)	Breast, ovarian, gastric, lung (NSCLC), uterine, serous endometrial carcinoma, colon, bladder, uterine cervix, head and neck, esophagus [66]
jun/fos (fra1)	Breast, lung, colon, prostate, brain, fibrosarcoma, glioma, Hodgkin lymphoma, myeloid leukemia, urothelial carcinoma of bladder, cervical, head and neck squamous cell carcinoma, gastric, ovarian, pancreatic, skin, tongue, liver, NSCLC [67]

src	SCLC, neuroblastoma, colon, breast, rhabdomyosarcoma [68]
ets1/2	Prostate [69], acute myelogenous leukemia, acute monocytic leukemia, breast [70], colorectal [71], astrocytoma, sarcomas, breast, ovarian, cervical, lung, squamous cell carcinoma, endometrial, T-leukemic cells [72]
myb	Breast, colon, pancreatic, glioblastoma, melanoma, head and neck, esophageal, vulvar, lacrimal glands, cutaneous T-cell lymphoma, T-cell acute lymphoblastic leukemia, acute myelomonocytic leukemia, acute myeloid leukemia, adenid cystic [73]
c-kit	Gastrointestinal stromal tumors (GIST), acute myeloid leukemia, seminomas, melanoma (some types) [74]
met	SCLC, mesothelioma, gastric, colon, rectal, renal, breast, ovarian, nervous system, epithelial tumors [75], cancer of unknown origin, hepatocellular, hereditary papillary renal, NSCLC, sporadic papillary renal [76]
fms	Acute myeloid leukemia, acute promyelocytic leukemia [77]
trk	Neuroblastoma, thyroid, breast, pediatric sarcomas, leukemias [78]
pokemon	B-cell/T-cell lymphomas, hepatocellular, glioma, NSCLC [79-83]

Conclusions

The main reason of the current research in regards to oncogenes role in carcinogenesis was to identify them as potential diagnostic and prognostic indicators in cancers and as possible novel therapeutic targets.However, it is essential to highlight that malignant tumors are not the result of a mutation in a single oncogene but they are the end-point of a pathway of gene activation which involves the oncogenes but also other important genes such as the tumor suppressor genes and genes implicated in cell cycle control, in addition to epigenetic phenomena such as DNA methylation and histone modifications

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