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Review Article

Markers Of Carcinogenesis

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Abstract

One of the theories of carcinogenesis is the theory of oncogenes. Oncogene is a gene responsible for the formation of growth factors. It is active during cell division. Its constant activity leads to the transformation of cell division into a malignant cell oncogene. In the absence of such transformation, oncogenes are in an inactive pro-oncogene state. Almost all the mentioned mechanisms of proto-oncogene activation have been described for human tumors, and, at different stages of cell transformation, expression of different oncogenes can be observed. At the same time, cellular oncogenes are characterized by tissue specificity - unequal sensitivity of cells of different tissues to transforming influence. One and the same oncogene can have different effects on cells of different origin, which indicates different molecular mechanisms of development of tumors of the same localization but different histogenesis. Proto-oncogenes are under the tight control of suppressor genes, or anti-oncogenes. Mutations of proto-oncogenes, which remove them from the influence of suppressor genes, contribute to the autonomy of their functioning and cause constant, "on-off" activity and the cell loses the ability to exit the mitotic cycle.

Key words: carcinogenesis; oncogene; markers

Summery

One of the theories of carcinogenesis is the theory of oncogenes. Oncogene is a gene responsible for the formation of growth factors. It is active during cell division. Its constant activity leads to the transformation of cell division into a malignant cell oncogene. In the absence of such transformation, oncogenes are in an inactive pro-oncogene state.

Proto-oncogenes are normal genes always present in any cell. The position, localization, function and chemical structure of most proto-oncogenes in human chromosomes have been determined; a significant proportion of them are located near chromosome breakpoints. Specific proteins - products of these genes involved in the realization of mitogenic signals have also been identified. [1] The functions performed by proto-oncogenes are very diverse. They completely determine the dynamics of development and existence of individuals throughout life. In norm, their activation is observed during reparative and proliferative processes, as well as during embryonic development. Proto-oncogenes play a key role in the formation of the cell response to cytokines and contribute to their production. They also control cell proliferation, mainly during the transition from one phase of the cell cycle to another. The key factor in the chain of signal transduction to proliferation within the cell are protein products of proto-oncogenes - proto-oncoproteins. [2] In a simplified form, the mechanism of signal transduction and control in the cell is a direct interaction of specific proto-oncoproteins in a strictly defined sequence. Thus, proto-oncogenes ensure the normal functioning of the signal transduction system in the cell, which creates conditions for its full existence in the environment and interaction with other cells. [3]

In normal cells, proto-oncogenes are inactive. In case of their structural changes (mutations), the level of their functional activity increases significantly. Such activated proto-oncogenes are called oncogenes producing corresponding oncoproteins. The latter are similar to normal proteins of proto-oncogenes, but with the difference that their production is independent of natural regulators. [4] The functions of oncoproteins are that they all, at various stages, disrupt the functional systems of normal cell growth and reproduction. Oncoproteins, in particular, activate cell proliferation, leading to the transformation of the cell into a malignant cell. These altered proteins belong to different signaling chains and are located at different steps of signal transduction in the cell. [5] Thus, most of the known oncogenes belong to key proteins of cellular signaling systems - growth factors, membrane and nuclear receptors, cytokines, etc. Some of these proteins have already been studied. The involvement of oncogenes in tumor genesis can be direct, when the protein produced by them participates in one or another stage of malignization, or indirect, when the protein has an activating or inhibitory effect on other genes. [6]

The names of oncogenes form abbreviations from the initial letters of the Latin names of the corresponding viruses from which they were originally isolated. There is currently no scientific classification of oncogenes. They are distributed according to the protein molecules produced by them, encoded by their cellular homologs - proto-oncogenes. [7] According to their similarity to the links of signals that stimulate mitotic activity, all proto-oncoproteins (or oncoproteins) are divided into homologs of growth factors and their receptors; transmitters of growth signals from receptors on DNA;

analogs of G-proteins (protein kinases) involved in the regulation of cell division, and others.

The study of transforming animal retroviruses led to the formation of the doctrine of oncogenes, but did not allow to explain the origin of human tumors, which are not caused by retroviruses. A natural question arose as to whether tumors of a non-viral nature contain oncogenes. It is now believed that proto-oncogenes can become oncogenes either when introduced into the cell by a virus or by carcinogenic influences that transform proto-oncogenes in situ into cellular oncogenes. [8] It has also been shown that any single oncogene is not capable of completely transforming a cell, but by acting cooperatively they can do so. Such cooperation is necessary because the functions of each oncogene are specialized; they form only some part of the new genotype and phenotype necessary for complete transformation. [9]

Currently, just over 100 different proto-oncogenes are known and are found on virtually all human chromosomes. It is estimated that there are about 20 potential oncogenes in each somatic cell. Since almost all known oncogenes encode proteins involved in essential cellular processes, it is believed that the number of identified oncogenes is approaching a natural limit limited by key mechanisms of known biochemical processes in cells.[10]

Proto-oncogenes are categorized into several groups:

1. growth factor receptors: HER-1 antibody, HER-2, HER-3,

2. responsible for intracellular transmission of growth signal: RET, K-RAS, N-RAS

3. transcription activation factors: C-MYC, C-MYC

4. apoptosis blockers: BCL-2, MDM2

5. growth factor: PDGF (Platelet-derived growth factor)

Growth factor receptors:

HER-1 antibody (human epidermal growth factor receptor 1, type 1):

The main function is as a receptor tyrosine kinase that binds EGF family ligands and activates several signaling cascades to convert extracellular signals into appropriate cellular responses. [11] Known ligands include EGF (Epidermal Growth Factor, epidermal growth factor receptor), TGFA/TGF-alpha (Transforming growth factor-alpha, transforming growth factor-alpha), AREG (amphiregulin), EPGN (epigen), BTC (Betacellulin), EREG (epiregulin) and HBEGF (heparin-binding growth factor). Ligand binding triggers homo- and/or heterodimerization of the receptor and autophosphorylation of key cytoplasmic residues. The phosphorylated receptor recruit's adaptor proteins such as GRB2 (The growth factor receptor-bound protein-2), which in turn activate complex downstream signaling cascades. Activates at least 4 major downstream signaling cascades including RAS-RAF-MEK-ERK modules (The Ras-RAF/Mitogen-activated protein kinase/ERK kinase (MEK)/extracellular-signal-regulated kinase (ERK)), PI3 kinase-AKT (phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT), phosphatidylinositol 3-kinase/protein kinase B), PLCgamma-PKC (phospholipase Cgamma (PLCgamma) and protein kinase C (PKC)) and STATs (Signal transducers and activators of transcription). [12] Can also activate the NF-kappa-B (nuclear factor kappa-light-chain-enhancer of activated B cells) signaling cascade. Also directly phosphorylates other proteins such as RGS16 (Regulator of G Protein Signaling 16), activating its GTPase activity and likely linking EGF receptor signaling to G-protein coupled receptor signaling. It also phosphorylates MUC1 and enhances its interaction with SRC (Proto-oncogene tyrosine-protein kinase) and CTNNB1/beta-catenin.

Isoform 2 may act as an antagonist of EGF action. [13]

Tissue specificity is ubiquitously expressed. Isoform 2 is also expressed in ovarian cancer.

Involved in diseases such as: lung cancer, inflammatory skin and intestinal diseases in neonates.

Belongs to the superfamily of protein kinases. Tyr family of protein kinases. EGF receptor subfamily. Contains 1 protein kinase domain. [14]

Phosphorylation by Ser-695 is partial and only occurs if Thr-693 is phosphorylated. Phosphorylation at Thr-678 and Thr-693 by PRKD1 inhibits EGF-induced activation of MAPK8/JNK1 (Mitogen-Activated Protein Kinase 8. Dephosphorylation by PTPRJ (Receptor-type tyrosine-protein phosphatase) prevents endocytosis and stabilizes the receptor at the plasma membrane. Autophosphorylation at Tyr-1197 is stimulated by methylation at Arg-1199 and enhances interaction with c. [15] Autophosphorylation at Tyr-1092 and/or Tyr-1110 recruits STAT3. It is dephosphorylated by PTPN1 and PTPN2 (Tyrosine-protein phosphatase non-receptor type 1 /2, Tyrosine-protein phosphatase non-receptor type 1 and 2).

Monoubiquitinated and polyubiquitinated upon stimulation with EGF, which does not affect tyrosine kinase activity or signaling capacity but may play a role in targeting to lysosomes. Polyubiquitin binding occurs primarily through Lys-63, but binding through Lys-48, Lys-11, and Lys-29 also occurs. Deubiquitination of OTUD7B prevents degradation. RNF115 and RNF126 are ubiquitinated. [16]

Methylation at Arg-1199 by PRMT5 stimulates phosphorylation at Tyr-1197.

It is secreted by cell membrane, endoplasmic reticulum membrane, Golgi apparatus membrane, nucleus membrane, endosome, endosome membrane and nucleus. In response to EGF, translocates from the cell membrane to the nucleus via the Golgi and ER (endoplasmic reticulum). Endocytosed upon ligand activation. It is localized together with GPER1 in the nucleus of estrogen agonist-induced cancer associated fibroblasts (CAFs). [17]

HER-2 (human epidermal growth factor receptor 2, type 2):

Primary function is performed by a proteintyrosine kinase that is part of several cell surface receptor complexes, but appears to require a coreceptor for ligand binding. An important component of the neuregulin-receptor complex, although neuregulins do not interact exclusively with it. [18] GP30 is a potential ligand for this receptor. It regulates the growth and stabilization of peripheral microtubules (MTS). Upon activation of ERBB2, the MEMO1-RHOA-DIAPH1 signaling pathway causes phosphorylation and thus inhibition of GSK3B (Glycogen synthase kinase-3Glycogen synthase kinase-3) at the cell membrane. This prevents phosphorylation of APC (Antigen presenting cells) and CLASP2 (Cytoplasmic Linker Associated Protein 2), allowing it to bind to the cell membrane. [19] In turn, membrane-bound APC allows MACF1 (Microtubule Actin Crosslinking Factor 1) to localize to the cell membrane, which is required for microtubule capture and stabilization.

In the nucleus is involved in the regulation of transcription. Binds to the 5'-TCAAATTC-3' sequence in the PTGS2/COX-2 (Prostaglandin-Endoperoxide Synthase 2) promoter and activates its transcription. [20] Involved in the activation of CDKN1A (cyclin-dependent kinase inhibitor 1A) transcription; STAT3 and SRC are involved in this function. Participates in rRNA gene transcription by RNA Pol I and enhances protein synthesis and cell growth. [21]

Does not have tissue specificity as it is expressed in a variety of tumor tissues, including primary breast tumors and tumors of the small intestine, esophagus, kidney, and oral cavity.

Involved in diseases such as: hereditary diffuse gastric cancer, glioma, ovarian cancer, lung cancer, and gastric cancer. [22]
Chromosomal aberrations involving ERBB2 (erythroblastic leukemia viral oncogene homolog 2) may be a cause of gastric cancer. Deletions in the 17q12 region cause transcripts to fuse with CDK12 (Cyclin-dependent

kinase 12), resulting in a CDK12-ERBB2 fusion leading to a truncated CDK12 protein that is not part of the ERBB2 structure.

Belongs to the protein kinase superfamily. [23] Tyr protein kinase family. EGF receptor subfamily. Contains 1 protein kinase domain.

Autophosphorylated. Autophosphorylation is trans-, i.e., one subunit of the dimeric receptor phosphorylates tyrosine residues on the other subunit. Binding to the ligand increases the phosphorylation of tyrosine residues. Signaling through SEMA4C promotes phosphorylation by Tyr-1248. It is dephosphorylated by PTPN12 (Protein Tyrosine Phosphatase Non-Receptor Type 12, Protein Tyrosine Phosphatase Receptor Type 12). [24]

It is localized in the cytoplasm, nucleus, and cell membrane.

HER-3:

Main function is binding and activation by neuregulins and NTAK.It is found in epithelial tissue and the brain. [25]

Defects in ERBB3 are the cause of fatal congenital contracture syndrome type 2, also called Israeli Bedouin multiple contracture syndrome type A. LCCS2 is an autosomal recessive neurogenic form of lethal neonatal arthrogryposis that is associated with atrophy of the anterior horn of the spinal cord. LCCS2 syndrome is characterized by multiple joint contractures, atrophy of the anterior horns of the spinal cord, and a unique feature of a markedly enlarged bladder. The phenotype suggests a neuropathic spinal cord etiology. [26] Belongs to the protein kinase superfamily. Tyr family of protein kinases. EGF receptor subfamily. Contains 1 protein kinase domain. Overexpressed in a subset of human breast tumors.

The cytoplasmic portion of the receptor can interact with the SH2 or SH3 domains of many signal transduction proteins. [27]

Binding to the ligand enhances phosphorylation of tyrosine residues and promotes its association with the p85 subunit of phosphatidylinositol-3-kinase.

It is secreted by the cell membrane. [28]

Proto-oncogenes are responsible for intracellular growth signaling:

RET (Proto-oncogene tyrosine-protein kinase receptor):

Performs receptor function with tyrosine-protein kinase activity.

Defects in RET may be a cause of colorectal cancer. [29]

Defects in RET are the cause of Hirschsprung's disease-it is a genetic disorder of neural crest development characterized by the absence of intramural ganglion cells in the hindgut, often leading to intestinal obstruction.

RET defects are the cause of medullary thyroid carcinoma (MTC), a rare tumor originating from the C cells of the thyroid gland. There are three known hereditary forms, which are transmitted in an autosomal dominant manner: (a) multiple neoplasia type 2A, (b) multiple neoplasia type IIB, and (c) familial RET, which occurs in 25-30% of RET cases and where RET is the only clinical manifestation. [30]

RET defects are the cause of multiple neoplasia type 2B, an uncommon inherited cancer syndrome characterized by a predisposition to CSF and pheochromocytoma, which is associated with a marfanoid habitus, mucosal neuromas, skeletal and optic nerve anomalies, and intestinal ganglioneuromas. The disease then progresses rapidly with the development of metastatic RET and pheochromocytoma in 50% of cases.

Defects in RET are a cause of predisposition to pheochromocytoma. A catecholamine-producing tumor of the chromaffin tissue of the adrenal medulla or sympathetic paraganglia. The main symptom reflecting increased secretion of adrenaline and noradrenaline is hypertension, which may be constant or periodic. [31]

RET defects are the cause of multiple neoplasia type 2A, also known as multiple neoplasia type 2, which is the most frequent form of medullary thyroid cancer (MTC). It is an inherited cancer syndrome characterized by MTC, pheochromocytoma and/or hyperparathyroidism.

RET defects are a cause of papillary thyroid carcinoma. PTC is a common thyroid tumor that usually arises as an irregularly shaped, solid or cystic mass from otherwise normal thyroid tissue. Papillary carcinomas are malignant neoplasms characterized by the formation of numerous, irregularly shaped, finger-like protrusions of fibrous stroma that is covered by a superficial layer of neoplastic epithelial cells. Note=Chromosomal aberrations involving RET are found in papillary thyroid carcinomas. [32] Inversion inv (10) (q11.2; q21) generates the oncogene RET/CCDC6(Coiled-coil domain-containing protein 6, coiled-coil domain-containing protein 6) (PTC1) (type Two C phosphatase); inversion inv (10) (q11. 2; q11.2) generates the oncogene RET/NCOA4 (Nuclear receptor coactivator 4) (PTC3); translocation t (10;14) (q11; q32) with GOLGA5(Golgin subfamily A member 5) generates the oncogene RET/GOLGA5 (PTC5); translocation t (8;10) (p21.3; q11. 2) with PCM1(Pericentriolar material 1) generates PCM1/RET fusion; translocation t (6;10) (p21.3; q11. 2) with RFP (Red fluorescent protein, red fluorescent) generates Delta RFP/RET oncogene; translocation t (1;10) (p13; q11) with TRIM33(E3 ubiquitin-protein ligase, E3 ubiquitin-protein ligase) generates TRIM33/RET (PTC7) oncogene; translocation of t (7;10) (q32; q11) with TRIM24/TIF1(Triple-stranded motif-containing 24, Triple-stranded motif-containing 24) generates TRIM24/RET (PTC6) oncogene. [33] The PTC5 oncogene was detected in 2 cases of PACT in children exposed to radioactive fallout after Chernobyl. A chromosomal aberration involving TRIM27/RFP is found in papillary thyroid carcinomas. Translocation t (6;10) (p21.3; q11.2) with RET. The translocation generates the TRIM27/RET and delta-TRIM27/RET oncogenes. [34]

Defects in RET are the cause of renal adysplasia, also known as renal agenesia or renal aplasia. Renal agenesia refers to the absence of one (unilateral) or both (bilateral) kidneys at birth. Bilateral renal agenesia refers to a group of perinatally fatal kidney diseases including severe bilateral renal dysplasia, unilateral renal agenesia with contralateral dysplasia, and severe obstructive uropathy."[35]

RET defects are the cause of congenital central hypoventilation syndrome, also known as congenital failure of autonomic control or Undine's curse. CCH is a rare disorder characterized by impaired respiratory control in the absence of neuromuscular or pulmonary disease and an identifiable brainstem lesion. The deficit in autonomic respiratory control results in inadequate or negligible ventilatory responses and arousal responses to hypercapnia and hypoxemia. [36]

Belongs to the superfamily of protein kinases. Tyr family of protein kinases. Contains 1 cadherin domain. Contains 1 protein kinase domain.

Autophosphorylated on C-terminal tyrosine residues upon ligand stimulation. Dephosphorylated by PTPRJ (Receptor-type tyrosine-protein phosphatase, Receptor-type tyrosine-protein phosphatase) on Tyr-905, Tyr-1015 and Tyr-1062.[37]

It localizes in the membrane.

K-RAS (Kirsten RAt Sarcoma (Kirsten Rat Sarcoma):

The function of Ras proteins is to bind GDP/GTP and have intrinsic GTPase activity.

Defects in K-RAS are the cause of acute myeloleukemia, a malignant disease in which the precursors of hematopoiesis are arrested early in development. [38]

Defects in K-RAS are the cause of juvenile myelomonocytic leukemia, which is a pediatric myelodysplastic syndrome that accounts for approximately 30% of pediatric myelodysplastic syndrome cases and 2% of leukemia cases. It is characterized by leukocytosis with tissue infiltration and in vitro hypersensitivity of myeloid precursors to granulocyte-macrophage colony-stimulating factor." [39]

Defects in K-RAS are a cause of Noonan syndrome type 3 (NS3). Noonan syndrome (NS) is a disorder characterized by dysmorphic facial features, short stature, hypertelorism, cardiac abnormalities, deafness, motor retardation, and bleeding diathesis. It is a genetically heterogeneous and relatively common syndrome, with an estimated incidence of 1 in 1000-2500 live births. Rarely, NS is associated with juvenile myelomonocytic leukemia. The inheritance of NS3 is autosomal dominant.

Defects in K-RAS are the cause of stomach cancer, also called gastric intestinal cancer or gastrointestinal cancer. Gastric cancer is a malignant disease that starts in the stomach, can spread to the esophagus or small

intestine, and can spread through the stomach wall to nearby lymph nodes and organs. It can also metastasize to other parts of the body. The term gastric cancer or gastric carcinoma refers to gastric adenocarcinoma, which accounts for the majority of all gastric malignancies. Two main histologic types of carcinomas are distinguished: diffuse type and intestinal type carcinomas. Diffuse tumors are poorly differentiated infiltrating lesions that result in gastric thickening. In contrast, intestinal tumors are usually exophytic, often ulcerated, and associated with intestinal metaplasia of the stomach, most often seen in sporadic disease.[40]

Defects in K-RAS are a cause of pilocytic astrocytoma (PA). Pilocytic astrocytomas are neoplasms of the brain and spinal cord originating from glial cells that range from histologically benign forms to highly anaplastic and malignant tumors.

Defects in K-RAS are the cause of CFC syndrome, also known as cardiofacial cutaneous syndrome. CFC syndrome is characterized by a distinctive facial appearance, heart defects, and mental retardation. Cardiac malformations include pulmonary artery stenosis, atrial septal defects, and hypertrophic cardiomyopathy. Some affected individuals have ectodermal abnormalities such as sparse, loose hair, hyperkeratotic skin lesions, and a generalized condition similar to ichthyosis. Typical facial features are similar to Noonan syndrome. They include a high forehead with supraorbital arches, hypoplastic supraorbital protrusions, slanted eye slits, depressed bridge of the nose, and ears with protruding spiracles angled posteriorly. The inheritance of CFC syndrome is autosomal dominant.[41]

Belongs to the small superfamily of the GTPase. Ras family.

Localizes in the cell membrane.

N-RAS:

The function of Ras proteins is to bind GDP/GTP and have intrinsic GTPase activity.

Defects in NRAS are the cause of juvenile myelomonocytic leukemia, which is a pediatric myelodysplastic syndrome that accounts for approximately 30% of pediatric myelodysplastic syndrome cases and 2% of leukemia cases. [42]

Defects in NRAS are the cause of Noonan syndrome type 6. Syndrome, characterized by dysmorphic facial features such as hypertelorism, downcast gaze, and low-set ears turned backwards. Other features may include short stature, short neck with webbing or excessive skin, cardiac abnormalities, deafness, motor retardation, and various intellectual disabilities.

It belongs to the small superfamily GTPase. Ras family. [43]

Palmitoylated by the ZDHHC9-GOLGA7(zinc finger DHHC-type palmitoyltransferase 9, Zinc finger DHHC-type palmitoyltransferase 9) complex. A continuous cycle of de- and re-palmitoylation regulates the rapid exchange between the plasma membrane and Golgi cells.

Localizes in the cell membrane, the membrane of the Golgi apparatus. Moves between the plasma membrane and the Golgi apparatus.

Transcription activation factors:

C-MYC:

Function is to participate in the regulation of gene transcription, binding DNA in a non-specific manner, but also specifically recognizes the 5'-CAC[GA]TG-3' basic sequence.

MYC overexpression has been implicated in the etiology of various hematopoietic tumors. [44]

A chromosomal aberration involving MYC may be responsible for a form of B-cell chronic lympholeukemia. BTG1-mediated translocation t (8;12) (q24; q22).

Defects in MYC are the cause of Burkitt's lymphoma (BL). A form of undifferentiated malignant lymphoma, usually manifested as an extensive osteolytic lesion of the jaw or as a mass in the abdomen. Chromosomal aberrations involving MYC are commonly found in Burkitt's lymphoma. Translocations t (8;14), t (8;22), or t (2;8) that map MYC to one of the immunoglobulins heavy or light chain gene loci.

Contains 1 basic helix-loop-helix-helix (bHLH) domain.

Phosphorylated by PRKDC (DNA-dependent protein kinase, catalytic subunit). Phosphorylation by Thr-58 and Ser-62 via GSK3(Glycogen synthase kinase 3, Glycogen synthase kinase 3) is required for ubiquitination and degradation by the proteasome. [45]

Ubiquitinated by the SCF(FBXW7) complex (F-box/WD repeat-containing protein 7, F-box/Company WD repeat-containing protein 7) upon phosphorylation by Thr-58 and Ser-62, leading to its degradation by the proteasome. In the nucleoplasm, ubiquitination is counteracted by USP28(ubiquitin specific peptidase 28, ubiquitin-specific peptidase 28) which interacts with FBXW7 isoform 1 (FBW7alpha), leading to its deubiquitination and preventing its degradation. In the nucleus, however, ubiquitination is not counteracted by USP28 due to the lack of interaction between FBXW7 isoform 4 (FBW7gamma) and USP28, which explains the selective degradation of MYC in the nucleus. Also polyubiquitinated by the DCX (Doublecortin, doublecortin) complex (TRUSS).

It is localized in the nucleus, its nucleoplasm, and the nucleolus. [46]

N-MYC (N-myc proto-oncogene protein):

Acts as a transcription factor.

Amplification of the N-MYC gene is associated with a variety of human tumors, most commonly neuroblastoma, where the level of amplification appears to increase as the tumor progresses.

Defects in MYCN are a cause of microcephaly- oculodigito-esophageal-duodenal syndrome, also known as oculodigito-esophagoduodenal syndrome. Microcephaly-oculodigestive-esophageal-duodenal syndrome is characterized by various combinations of esophageal and duodenal atresia, microcephaly, learning disability, and limb malformations. Heart and kidney malformations, spinal anomalies, and deafness have also been described.[47]

Defects in MYCN are a cause of microcephaly and digital anomalies with normal intelligence.

Contains 1 basic helix-loop-helix-helix (bHLH) domain.

Expressed during intrauterine development.

Localizes in the nucleus.

Blocker of apoptosis:

BCL-2(B-cell lymphoma 2, Bcl-2(B-cell lymphoma 2) protein)):

Main function is to suppress apoptosis in various cell systems including factor-dependent lymphohematopoietic and nerve cells, regulation of cell death by controlling mitochondrial membrane permeability, inhibition of caspase activity either by preventing the release of cytochrome c from mitochondria and/or by binding to factor, APAF-1(Apoptotic protease activating factor 1)(Apoptotic protease activating factor 1) attenuation of inflammation by disrupting NLRP1-inflammasome activation, hence CASP1 activation and IL1B(Interleukin-1 beta) release.

It has no tissue specificity as it is expressed in various tissues. [48]

A chromosomal aberration involving BCL2 has been found in chronic lympholeukemia. Translocation t(14;18) (q32;q21) with immunoglobulin gene regions. BCL2 mutations found in non-Hodgkin's lymphomas carrying the chromosomal translocation can be attributed to a mechanism of somatic Ig hypermutation resulting in nucleotide transitions.

It belongs to the Bcl-2 family.

The BH1 and BH2 domains are required for interaction with BAX and for anti-apoptotic activity.

The BH4 motif is required for antiapoptotic activity and for interaction with RAF1 and EGLN3.

The loop between the BH4 and BH3 motifs is required for interaction with NLRP1.[49]

Phosphorylation/dephosphorylation on Ser-70 regulates anti-apoptotic activity. Growth factor-stimulated phosphorylation of Ser-70 by PKC is required for anti-apoptotic activity and occurs during the G2/M phase of the cell cycle. In the absence of growth factors, BCL2 appears to be phosphorylated by other protein kinases such as ERKs and stress-activated kinases. MAPK8/JNK1(Mitogen-activated protein kinase 8, Mitogen-activated protein kinase 8) is phosphorylated at Thr-69, Ser-70 and Ser-87, which stimulates starvation-induced autophagy. Dephosphorylated by protein phosphatase 2A (PP2A) (Protein phosphatase 2).

Proteolytically cleaved by caspases during apoptosis. The cleaved protein, lacking the BH4 motif, has pro-apoptotic activity and causes the release of cytochrome c into the cytosol, promoting further caspase activity. [50]

PARK2 is monoubiquitinated, leading to an increase in its stability. SCF(FBXO10) is ubiquitinated by SCF, leading to its degradation by the proteasome.

Localizes on the mitochondrial outer membrane, nucleus membrane and endoplasmic reticulum membrane.

MDM2(Mouse double minute 2 homolog):

Ubiquitin E3 is a protein ligase that mediates ubiquitination of p53/TP53 leading to its degradation by the proteasome. Inhibits p53/TP53- and p73/TP73-mediated cell cycle arrest and apoptosis by binding its transcription activation domain. Also acts as an E3 ubiquitinligase relative to itself and ARRB1.[51] Permits nuclear export of p53/TP53. Promotes proteasome-dependent ubiquitin-independent degradation of retinoblastoma RB1 protein. Inhibits DAXX-mediated apoptosis (death domain associated protein) by inducing its ubiquitination and degradation. A component of the TRIM28/KAP1-MDM2-p53/TP53 complex involved in p53/TP53 stabilization. Also, a component of the TRIM28/KAP1-ERBB4-MDM2 complex, which links growth factor and DNA damage response pathways.

Does not have tissue specificity as it is expressed in a variety of tumor tissues. The Mdm2-A isoform, Mdm2-B isoform, Mdm2-C isoform, Mdm2-D isoform, Mdm2-E isoform, Mdm2-F isoform, and Mdm2-G isoform are observed in a number of cancers, but are absent in normal tissues. [52]

It appears to be amplified in some tumors (including soft tissue sarcomas, osteosarcomas, and gliomas). A higher frequency of splicing variants lacking p53 binding domain sequences has been found in advanced stage and high malignancy ovarian and bladder carcinomas. Four splice variants demonstrate loss of binding to p53.[53]

Belongs to the MDM2/MDM4 family. Contains 1 zinc finger of the RanBP2 type. Contains 1 RanBP2-type zinc finger. Contains 1 SWIB domain.

Region I is sufficient to bind p53 and inhibit its G1 arrest and apoptosis functions. It also binds p73 and E2F1. Region II contains most of the central acidic region required for interaction with ribosomal protein L5 and a putative C4-type zinc finger. The zinc finger domain, which coordinates two zinc molecules, specifically interacts with RNA whether zinc is present or not and mediates MDM4-mediated hetero-oligomerization. It is also required for its E3 ubiquitin-ligase activity toward p53 and itself.

Phosphorylated in response to ionizing radiation in an ATM-dependent manner.

Autoubiquitinated, leading to proteasomal degradation. Deubiquitinated USP2(Ubiquitin carboxyl-terminal hydrolase 2, Ubiquitin carboxyl-terminal hydrolase 2), leads to its accumulation and enhances deubiquitinylation and degradation of p53/TP53. Deubiquitinylated by USP7; leading to its stabilization.

Localizes in the nucleoplasm and nucleolus of the nucleus accumbens, cytoplasm. Expressed predominantly in the nucleoplasm. Interaction with ARF(P14) leads to localization of both proteins in the nucleus. Nucleus localization signals in both ARF(P14) and MDM2 may be required for efficient nucleus localization of both proteins. It colocalizes with the A isoform of RASSF1(Ras association domain-containing protein 1, Ras association domain-containing protein 1) in the nucleus.[54]

Growth factors:

PDGF (Platelet-derived growth factor):

A potent mitogen for cells of mesenchymal origin. Binding of this growth factor to its affinity receptor induces a variety of cellular responses. It is released by platelets upon wounding and plays an important role in stimulating the growth of neighboring cells and thus healing the wound. It is activated by proteolytic cleavage and this active form acts as a specific ligand for the beta platelet-derived growth factor receptor. Induces macrophage recruitment, increased interstitial pressure, and blood vessel maturation during angiogenesis.

Expressed at high levels in the heart, pancreas, adrenal gland, and ovaries and at low levels in the placenta, liver, kidney, prostate, testes, small intestine, spleen, and colon. In the kidney, it is expressed by visceral epithelial cells of the tubules. Widespread expression is also seen in medial smooth muscle cells of arteries and arterioles and in smooth muscle cells of straight vessels in the medulla. It is expressed in the adventitial connective tissue surrounding the adrenal artery. In chronic obstructive nephropathy, there is persistent expression in tubular visceral epithelial cells and vascular smooth muscle cells, as well as de novo expression by periglomerular interstitial cells and some neointimal cells of arteriosclerotic vessels. Expression in the normal prostate is seen predominantly in the glandular mesenchyme, whereas expression is elevated and more abundant in prostate carcinoma. Expressed in many cell lines derived from ovarian, lung, kidney and brain cancers.

Belongs to the PDGF/VEGF (Vascular endothelial growth factor) family of growth factors. Contains 1 CUB domain.

It is undetectable in the earliest stages of glomerulogenesis and is not found in metanephric blastema or surrounding cortical interstitial cells. In later stages of glomerulogenesis, it is localized in epithelial cells transitioning from early developing comma and S-stage nephrons to visceral epithelial cells of differentiated tubules. In the developing pelvis, it is expressed on the basal membrane of immature collecting ducts and by putative fibroblastic cells in the interstitium.

Proteolytic deletion of the N-terminal domain of CUB releasing the core domain is required to unmask the receptor-binding epitopes of the core domain. Cleavage after Arg-247 or Arg-249 by plasminogen activator urokinase results in the active form.

Does not have a specific cellular localization.

It should be noted that chromosome rearrangements that cause tumor development do not necessarily affect only proto-oncogenes. Other genes encoding target proteins of oncogene products may also undergo changes. A number of oncogenes are activated through qualitative changes, where a change in the amino acid sequence of an oncoprotein is accompanied by an increase in its enzymatic activity (e.g., mutations in RAS family oncogenes). Activation of oncogenes can be caused by agents that do not directly damage DNA but trigger a chain of reactions leading to mediated activation of proto-oncogenes. These carcinogens have been termed epigenetic carcinogens.[55]

Almost all the mentioned mechanisms of proto-oncogene activation have been described for human tumors, and, at different stages of cell transformation, expression of different oncogenes can be observed. At the same time, cellular oncogenes are characterized by tissue specificity - unequal sensitivity of cells of different tissues to transforming influence. One and the same oncogene can have different effects on cells of different origin,

which indicates different molecular mechanisms of development of tumors of the same localization but different histogenesis.

Proto-oncogenes are under the tight control of suppressor genes, or anti-oncogenes. Mutations of proto-oncogenes, which remove them from the influence of suppressor genes, contribute to the autonomy of their functioning and cause constant, "on-off" activity and the cell loses the ability to exit the mitotic cycle.

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