LITERATURE REVIEW

Cancer - dysregulation of the cell cycle and transduction of cascade signals

Akhmad Madaminov[1], Akbar Khasanov[1], Shuhrat Khatamov[1], Otabek Abdurakhmonov[1], Anvar Amonov[1], Zohir Shukurov[1], Murod Khudayorov[2], Rahim Bekmirzaev[1], Latif Nishonboev[1]

[1]National Cancer Research Center of Uzbekistan, Department of Head and Neck Surgery, Tashkent, Uzbekistan

[2]Tashkent Medical Academy, Department of Oncology, Tashkent, Uzbekistan

ABSTRACT

According to scientific data, cancer is a very ancient disease, and along with the perfection of humanity it becomes more progressive. The development of technologies that detect molecular changes in the pathogenesis and subsequent development of carcinogenesis has led to the beginning of a new era in oncology. The cell cycle is tightly controlled by a group of protein kinases, including cyclin and cyclin-dependent kinases. These events occur in a strictly regulated time sequence supported by consistent restriction points. p53, p21, p16, retinoblastoma (and other proteins), cyclins and cyclin-related kinases repair DNA before the cell cycle enters the phase of synthesis and mitosis. Loss of regulatory activity of p53 and pRB, stable activation of E2F stimulates uncontrolled cell proliferation, leading to neoplastic cell growth. The Ras/Raf/MEK/ERK signalling pathway is also a complex network of sequentially activated proteins that play a major role in the onset and development of cancer. It can regulate not only the biological functions, such as cell proliferation, cycle regulation, cell differentiation, apoptosis and tissue formation, but it is also associated with tumor development. Stable mutations in the genome or defects in the epigenome lead to dysregulation in the normal biological cycle of the cell, underlying DNA chain damage or dysfunction in the control system, determined by various types of carcinogenic factors, both known and unknown.

KEYWORDS: carcinogenesis, gene mutation, cell cycle, cyclin, p53, signal transduction.

INTRODUCTION

The human body is made up of cells that combine all the features of life, controlled by a complex system, and important biological processes take place between various factors in the external environment. A cell is a functional unit that provides the transmission of genetic information, metabolism, energy exchange, and the integrity of life. Single-celled individuals found in nature have a very simple structure and the property of living autonomously. Cancer cells may also resemble amoebae in some physiological aspects such as, simplicity of differentiation, lack of definitive form, dynamic activity of cytoplasm, high demand for trophic and plastic primary substrates. The presence of these specific features is also reflected in the appearance of the cell.

Why do cancer cells live independently of the system that controls the vital activity of the human body, multiply non-stop rapidly, and are more viable than healthy cells? According to historical sources, around 400 BC, the ancient Greek scientist Hippocrates identified a disease that resembled a crab that develops from a disruption of the circulatory system of black bile in the human body and moves in different directions. Abu Ali ibn Sina (980-1037) stated the following about the development of cancer: "Not all causes affect the body, and no cause can cause disease without the body's sensitivity"[1]. In 1931, the German physiologist Otto Heinrich Warburg supported the hypothesis that the energy expended in the growth of cancer cells was formed mainly as a result of anaerobic breakdown of glucose (glucose fermentation). This differs from healthy cells in that pyruvic acid is

Corresponding author: Akhmad Madaminov, National Cancer Research Center of Uzbekistan; Ministry of Health of Uzbekistan; Republic of Uzbekistan, 100174 Tashkent, Farobi, 383
ORCID: https://orcid.org/0000-0003-0064-3746
e-mail: akhmad.madaminov@inbox.ru
Received for publication: April 16, 2021 / **Accepted:** May 20, 2021

formed as a result of glucose oxidation in mitochondria. This means that cancer is an evolutionary ancient disease, and along with the civilization of life, this disease is also on the rise.

At a time when almost a quarter of the 21st century is passing and innovative technologies are being widely used in medicine, what has been achieved by humanity in this regard? Nowadays, finding a gene in cancer, finding a target for that gene is a bright sign that a new era has arrived in modern oncology. Many scientific studies contain various research findings or hypotheses about the causes of cancer and the mechanisms that affect them, but many questions on this topic still remain unclear. Genetic instability, which is the main cause of cancer heterogeneity, persistent disruption of the sequence of DNA nucleotides sequences, and chromosome rearrangement pose significant obstacles to the development of more effective treatments.

GENETICS AND EPIGENETICS

In 2003, the Human Genome Research Project completed many years of research by scientists from around the world to decipher the structure of the human genome, which is made up of deoxyribonucleic acid (DNA) molecules and identified between 20,000 and 25,000 genes[2]. The human genome is made up of about three billion DNA base pairs that make up all the chromosomes. Base pairs (bp) are the hydrogen compounds of adenine-thymine and guanine-cytosine in the DNA helix[3]. Genome units of measurement consists in one million nucleotide base pairs (bp) equal to 1 Mb (mega base), 978 Mb equal to 1 pictogram (pictogram = $1*10^{-12}$ grams). Relevant genes are responsible for cell growth, differentiation, proliferation, viability, programmed death (apoptosis), response to external factors and other important life activities, and information is transmitted through ribonucleic acid (RNA) and proteins[4]. Suppression, repression and regulation of encoded genes are controlled using the epigenome (epigenetics). Epigenetics is a relatively new field that has not yet been as widely studied as genetics, which is understood as a branch of genetics that studies the hereditary changes in gene activity during organism development or cell division. Literature data estimates that 5% of human cancers are caused by viruses, 5% by radiation, and the remaining 90% by chemicals[5]. About 30% of them are due to the use of tobacco products, the rest are related to nutrition, lifestyle and environment. The chemical carcinogens or their derivatives are highly reactive electrophiles (donor-acceptor mechanism) with electron (*e*–) deficient atoms that can easily react with electron-rich nucleophiles in the cell. DNA consists of many nucleophilic centers (NH_2-groups) in which DNA-damaging substances can form appendages (DNA-adducts) through one or more covalent bonds. With the advent of new technologies in molecular analysis, gene expression profiling, gene network, microRNA, gene discovery and pathway analysis, integrated transcriptome collection, and two genetic carcinogenesis using ChIP-Seq (chromatin immunoprecipitation sequencing, cystrom) has been shown to be more complex than clone evolution[6,7]. The modern multi-stage model of carcinogenesis involves at least 80 mutations or changes in the cancer gene, about a dozen of which are "drivers" of cancer development processes. The process of carcinogenesis can occur due to changes in four categories of genes, namely, activation of oncogenes, inactivation of suppressor genes, annulation of apoptosis and DNA repair genes[8,9].

The development of multi-stage carcinogenesis at each stage of cell proliferation (initiation, stimulation, progression) is inextricably linked with the mechanism of positive or negative interaction of oncogenes, suppressor genes, growth factors and their associated receptors[3]. The prevalent model of the cell cycle consists of a series of transitions and, at some control points, the restriction criteria under the influence of control factors must be followed before the cell moves to the next stage[10]. The cell cycle consists of S (DNA synthesis) and M (mitosis) phases, separated by two disruption phases (G1 and G2)[11]. It is tightly controlled by a group of heterodimeric protein kinases, including cyclin and cyclin-dependent kinases (Cdk), which regulate the progression of the cell cycle and contain catalytic subunits[12]. There are many combinations of cyclin-dependent kinase complexes characterized by the expression and activity of patterns at each stage of the cell cycle[13]. According to scientific data, more than fifteen classes of cyclins are described (including A, B, C, D, E, F, H, K, L, T and Y), whose function is to control and repair DNA synthesis from cell cycle control, transcription, proteolysis, up to RNA splicing and cell differentiation[14]. Specific cycles predominate in the movement of each cell cycle, for example, cyclin D in phase G1, cyclins E and A in phase S, and cyclins A and B in phase G2 / M. The peak of synthesis and activity of cyclins D and E regulates the transition from phase G1 to phase S. Cyclins A and B manifest themselves at the maximum level of exposure at the end of the cycle and are considered regulators of the transition from G2 to mitosis. When cyclins rise to maximum activity according

to the phase of the cell cycle, they lead to phosphorylation of various specific-target molecules (cyclin-dependent kinases). These events occur in a strictly regulated time sequence supported by consistent restriction points. The presence of control components at these restriction points allows DNA repair by slowing down the process before moving on to the next cycle. Replication of a damaged genetic pattern will undoubtedly lead to irreversible chromosome aberrations and high-level mutations[10,13,15]. The two main restriction points are particularly important after DNA damage and are established in phases G1 (before DNA replication) and G2 (before chromosome segregation) (Figure 1).

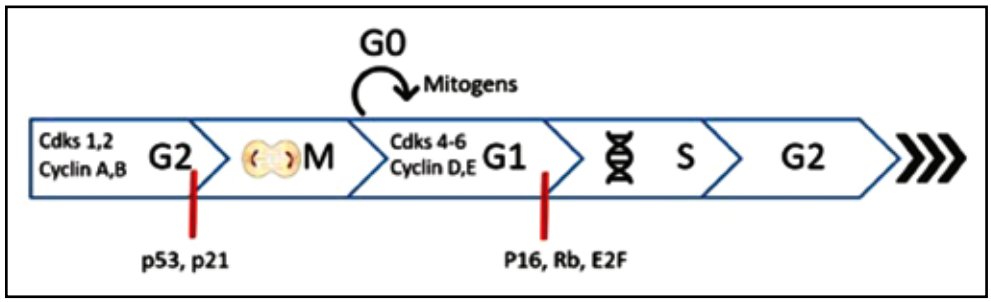

Figure 1. Control of the cell cycle (red line: restriction point "checkpoint").

Loss of the G1 restriction point causes genome instability during the interaction of unrecoverable DNA with the DNA replication mechanism, leading to deletion-type mutations and aberrant gene amplification[16]. Inactivation of the G1 restriction point serves as an initial stage, prone to unregulated cell growth (initiation), increasing the likelihood of subsequent genetic changes and creating a fully developed neoplastic phenotype. Control at the G1 restriction point depends on the D1 cyclin (transition phase from G1 to S) and the E cyclin (mid-phase S). Hyperexpression of D1 or E cyclin and subsequent activation of D1 cyclin and E cyclin/ Cdk complexes lead to phase C transition and shortening of G1 time[10,11,16,17]. Cyclin D1 hyperexpression is observed in many dangerous human cancers, including breast and lung small cell carcinomas, sarcomas, melanoma, V-cell lymphomas and head-neck squamous cell carcinomas. The cyclin D1/Cdk4 complex is involved in the phosphorylation of pRB, a gene product responsible for retinoblastoma[18]. The pRB protein acts as a negative regulator of the expression of certain genes by forming a complex with DNA-binding proteins belonging to the E2F family[19]. In the G0 phase of the cell (where division has stopped), low-phosphorylated pRB binds to proteins belonging to the E2F group, leading to E2F-mediated transcriptional repression. High phosphorylation of pRB protein under the influence of cyclin / Cdk complexes leads to dissociation of E2F protein and transcription of genes that in turn help to enter the S phase[10]. Thus, insufficient phosphorylation of pRB keeps cells in G1 (or G0), while phosphorylation inactivates pRB and allows it to exit G1. pRB inactivation is most commonly seen in retinoblastoma, osteosarcoma, carcinoid tumors, and non-small cell lung cancer[20].

In addition to cyclin and cyclin/Cdk complexes, the p53 gene suppressor is also essential to maintain the G1 phase after DNA damage. A mutation in the p53 locus is the most common genetic change associated with cancer. The p53 protein can be divided into three main components: the transactivation amino-terminal domain, the site-specific hyperreactive central part of the DNA sequence, and the multifunctional carboxy-terminal domains (tetramerization). Many p53 mutations involve highly conservative segments of the DNA-specific central part. Inactivation of p53 allows the synthesis of damaged DNA and increases the frequency of some types of mutations[3,16,21]. This high frequency has been observed as a result of various mechanisms of DNA damage, such as ionizing radiation (helix rupture), alkylation with methyl methanesulfonate, ultraviolet radiation (photodimers), and various environmental carcinogens. One of the key roles of p53 is to ensure that cell growth stops in G1 in response to genotoxic damage and recovers before DNA replication. The natural type p53 (wild type) is usually kept stable at very low concentrations due to the shortness of the half-life (half-decomposition)[21]. However, it stabilizes and accumulates in cells that have undergone DNA damage or respond to certain forms of stress. After DNA damage, p53 binds to specific consensus components, activating the transcription of several

genes of the lower order. One of these genes encodes the p21 protein[22]. The p21 gene belongs to the family of negative regulators of the cell cycle, which act as molecules that inhibit cycle-related kinases. The genes encoding these proteins are called CKI (Cdk inhibitor, CKI, CDI, CDKI) genes. The negative regulators and the cyclin / Cdk units form stable complexes and inactivate them. The p21 cycle inactivates the E-Cdk2, cyclin A-Cdk2, and cyclin D1-, D2-, and D3-Cdk4 complexes, thereby inhibiting the phosphorylation of pRB and preventing the cell cycle from exiting G1[23]. The p53 protein also activates the VAX (Bcl-2-Associated X protein) gene, which is involved in regulating apoptosis. Apoptosis is the mechanism by which cells stop the life cycle, leading to "programmed death". Apoptotic cells contract in response to DNA damage and chromosome condensation. These changes prevent the replication of genetically damaged cells to an irreversible extent. During the mitotic phase, chromatin must be evenly distributed to the daughter cells, but DNA replication must be completed before segregation occurs and all damaged parts of the DNA must be restored. If mitosis occurs when DNA is damaged or during replication, it can lead to genome fragmentation and loss of genetic material[24]. Genome stability is controlled by a large network of proteins called DNA damage response (DDR), which detects DNA damage and facilitates repair. Activation of DDR proteins leads to activation of transducer kinases CHK1 and CHK2 and other effector proteins. DDR can respond to DNA damage by disrupting phases G1, S, or G2[10,17].

The p53 protein controls its work by activating the MDM2 gene. The product encoded by MDM2 is a "zinc finger" protein (mdm2) that contains the p53 site-specific binding component. The mdm2 protein binds to p53 acting as a negative regulator, inhibiting the transcriptional activity of the natural type p53 and forming a feedback autoregulation ring. The presence of a carboxyl-terminal domain of mdm2, which binds site-specific to the pRB and limits its function, has been identified. Similar to the hyperexpression of mdm2, some virus oncoprotein products inactivate both p53 and pRB and exhibit a potential relationship between p53 and pRB in cell cycle management, apoptosis, and tumor development[21]. The cell cycle and its regulatory proteins change in favour of many viral agents. Activation of the human body cell replication mechanism is required for viral genome replication. It has been shown to alter the regulatory function of p53 and pRB in response to the action of several viral proteins. The SV40 virus inactivates it by binding to the major T antigen, the adenovirus EIB protein and the human papilloma virus E6 protein p53. Similarly, SV40 major T antigen, adenovirus EIA protein and human papilloma virus E7 protein form a complex with insufficiently phosphorylated pRB, leading to inactivation of pRB and cell immortalization. Highly altered tumor virus strains encode proteins that bind and inactivate p53 and pRB. When growth control is impaired as a result of inhibition of pRB in normal cells, apoptotic death occurs by the normal p53 side. Loss of regulatory activity of p53 and pRB and the stable activation of E2F stimulate uncontrolled cell proliferation, leading to neoplastic cell growth. The nature and high frequency of p53 and pRB mutations in primary tumors make them prototypes of tumor suppressor genes. In addition, the detection of mutations in the p53 and pRB genes and changes in the expression of their coded products have clinical prognostic significance in the identification of specific types of cancer[25]. Mutant gene p53 and Ki67 hyperexpression in osteosarcoma cells was found to alter treatment efficacy in 37.4% of patients[26].

Thus, cell growth and its management are complex biological processes that occur through site-specific binding of factors belonging to relevant groups to each other. These factors, which have a well-defined trajectory of impact, are coded products of the cell genome. In this sense, the initiating factors of molecular mechanisms activated in a cancer cell are structural changes in the DNA matrix or functional defects in the epigenome.

SIGNAL TRANSDUCTION CASCADES

The composition, structure, properties and events of cells are related to the molecules and the chemical reactions that take place between them. Due to the coordination of these biochemical processes that take place, the integrity of the organism is maintained. The same integration system is based on intercellular and intracellular signal transduction. Signal transduction is any process that transmits one type of signal or stimulus in a cell to another. Intracellular signal transduction is a chain of reactions carried out sequentially by enzymes, the primary effector proteins being activated after receptor stimulation, and some by secondary messengers. The duration of such processes usually occurs at high speeds: milliseconds for ion channels, minutes for protein kinases[27]. As the number and activity of protein molecules and other substances involved in signal transduction gradually increase, the primary effector increases as it moves away from the signal. In the same way,

a relatively weak effect on cell receptors can also trigger a significant response. There are several types of intracellular signalling cascades (PI-3-Kinase/Act, JAK-STAT, NF-kB, heterotrimer G-proteins, Ras-MAPK/ERK, Wnt, Hedgehog, Fas, TREM2) which activate as a result of the stimulus factor, then transmit the cascade signals to the genetic apparatus in the nucleus. Another mechanism that causes the acceleration of the process of carcinogenesis is the hyperactivation of these signal-transmitting cascades[28]. Nuclear signals from activated cascades cause abnormal changes in the genome or epigenome, which in turn negatively affects cell reproduction and leads to the development of cancer cells. The reception of primary signals by the cell is ensured by ultra-correct binding of special proteins - receptors with ligands. Cell receptors are divided into the following types: membrane (tyrosine kinase, G-protein, ion channels), cytoplasm and nuclear receptors[7,29]. Once the ligand binds to the membrane receptor, it transmits the information to the protein components of the membrane, which provide signal generation across the cascade[30]. Membrane proteins of the signal transduction cascade are divided into receptor-bound transduction-protein and transduction-protein-associated catalytic domain-containing proteins that activate secondary effectors that transmit information into the cell[31,32].

Scientists from the Department of Molecular and Cellular Biology at Baylor College of Medicine in Houston, United States, studied the effects of transcriptome and ChIP-Seq data on transcriptional regulation of cell signalling pathways. The vast body of accurate data and hypotheses obtained led to the generation of the Signaling Pathways Project (SPP). According to the study, cell signalling pathways consist of points that are classified into three major categories (receptors, enzymes, transcription factors) and small biologically active molecules (bioactive small molecules, BSMs) that modulate their activity. Based on the SPP knowledge base, a range of signal path modules and bionam samples was developed, cell receptors were classified according to the International Pharmacological Union (IUPHAR), enzymes by the International Union of Biochemistry and Molecular Biology (IUBMB) and transcription factors according to the TF-Class[7]. In addition, the classification of biological tissues and cell lines according to the physiological system of their organs and origin helps to understand the laws of tissue-specific transcriptional regulation[7]. In ChIP-Seq experiments and integrated transcriptomes (expression sequence and RNA-Seq), the interaction of signal path nodes in transcription regulation can be determined by sequential placement (signature consensus) of parameters based on target genome promoter employment and differential expression. Metabolic signals with a biological terminal point connect receptors, enzymes and transcription factors through a series of interrelated interactions. These three categories of the signal pathway act as convergence and integration points, ensuring divergence and distribution on the one hand, and an appropriate response of any cell to afferent metabolic signals on the other. The intracellular signalling cascade activated under the influence of extracellular mitogenic factors has a motivational vector consisting of sequential activation of kinase proteins.

Ras/Raf/MEK/ERK SIGNAL CASCADE

Mitogen-activated protein kinase (MAPK) cascades are one of the main signalling pathways that control a wide range of biological processes, including cell proliferation, differentiation, apoptosis and stress reactions[33-36]. Extracellular signal-regulated kinase 1/2 (extracellular signal-regulated kinase, ERK) belongs to the MAPK family and is the main effector in cascade signals[37]. These cascades transmit signals by sequential activation of three to five protein kinase layers known as MAPK kinase kinase kinase (MAP4K), MAPK kinase kinase (MAP3K), MAPK kinase (MAPKK), MAPK, and MAPK-activated protein kinases (MAPKAPK)[38]. The first three central layers are considered as the main block, and the last two appear in some cascades, which may vary according to cells and stimuli. Based on the components in the MAPK layer, four MARK cascades are distinguished: ERK 1/2, c-Jun N-terminal kinase (JNK), p38 MAPK and ERK5.

The ERK cascade contains several kinases in the MAP3K layer (mainly Rafs), including the Ras/ Raf/MEK1/2 MAPKK layer, the ERK 1/2 MAPK layer, and several MAPKAPKs in the next layer (ribosomal s6 kinases, interacting with MAP kinases), affecting serine/threonine-protein kinases, cytosol phospholipase A2, and mitogen and stress-activated protein kinases[39]. ERK cascades are highly regulated cascades that involve cell proliferation and differentiation. These regulatory factors affect bispecific phosphatases, carcass proteins (cascade-forming), signal duration and intensity, and dynamic subcellular localization of cascade components[40]. Excessive activation of proteins and kinases located in the upper layer of the ERK pathway has been shown to cause cancer, in-

flammation, neurological and other diseases[41-44]. Dysfunction in the Ras-ERK pathway is a trigger factor in the development of many cancers, mutations in the activating driver genes of this pathway being the most common oncogenic factor in all cancers[45]. In cancer, the different components in the cascade are highly variable. According to Maik-Rachline G, Hacohen-Lev-Ran A, Seger R, driver mutations in Ras (mainly K-ras) are the most common mutations in cancer, occurring in almost 30% of cancers and 10% of cancer patients[27]. Raf mutations (particularly B-Raf) have been identified in approximatively 8% of cancers[2,46]. ERK is a type of serine / threonine protein kinase that transmits mitogenic signals. ERK is usually located in the cytoplasm, enters the nucleus after activation, and regulates the activity of transcription factors and gene expression. Analysis of artificial cloning and sequencing showed that the ERK family consists of ERK 1, 2, 3, 4, 5 and 6[47]. Although ERK1 and ERK2 are two important members of the MAPK/ERK pathway, ERK5 is also highly active in transcription management. The S-terminal of ERK5 includes the nuclear localization signal (NLS), two proline-rich sites and the transcription activation domain (TAD). This structural difference allows the active ERK5 to spontaneously phosphorylate its C-terminal TAD, a unique feature that directly controls gene transcription. In the non-phosphorylated state, ERK5 is in an inactive conformation and its N- and C-terminal domains are bound to each other in the cytoplasm. Activation of MEK5 induces an open conformation of ERK5, opens NLS, softens self-inhibition and induces nuclear translocation of ERK5[48-50].

Many stimulants, such as growth factors, cytokines, viruses, G-protein-bound receptor ligands and oncogenes, activate the ERK pathway[40]. The main molecules in the ERK/MAPK signalling pathway mainly include Ras small G proteins and the lower layer Raf kinase, MEK1/2 and ERK1/2. Ras is the most conservative product of the ras gene family encoded by *Ha-ras*, *Hi-ras*, and *N-ras* oncogenes. Raf kinase is a derivative of *raf* oncogenes. MEK1 and MEK2 are rare bispecific kinases that activate ERK by phosphorylation of two regulatory sites Tyr 204/187 (tyrosine) and Thr 202/185 (threonine)[51]. Ras is a small G protein located at the apex of the Raf-MEK-ERK pathway that is a product of *ras* oncogenes (retrovirus-associated DNA sequences). It has a conformation associated with active GTP (guanosine triphosphate) and a conformation associated with inactive GDP (guanosine diphosphate)[52]. The protein acts as a molecular binder by switching between two conformations to regulate signal transduction. Ras is activated by many stimulatory factors, such as epidermal growth factor (EGF), tumor necrosis factor, protein kinase activators C (PKC), and members of the Src family. After the extracellular signal binds to the receptor, the protein 2 (Grb2) bound to the growth factor receptor binds to the activated receptor and interacts with the proline-rich tandem site at the S-terminal of SOS (Son of sevenless) to form the receptor-Grb2-SOS complex[31,40]. Binding of the SOS to the phosphorylated Tyr site in the receptor or receptor substrate protein results in translocation of the cytoplasmic SOS to the membrane, resulting in a high SOS concentration around the Ras. SOS and Ras-GDP stimulate the replacement of GDP in Ras with GTP and thus activate Ras to start the Ras pathway[53,54].

Raf (rapidly accelerated fibrosarcoma) protein kinase is a protein composed of 648 amino acids encoded by the *raf* gene located on human 3rd chromosome and has a molecular weight of 40–75 kDa ge. Serine/threonine exhibits protein kinase activity after binding to Raf Ras. Its molecular structure includes three conservative regions: Conserved region (CR) 1 (located in amino acids 61-194), CR2 (located in amino acids 254-299) and CR3 (located in amino acids 335-627). The CR1 cysteine-rich zinc located in the amino-terminal has a zinc-like structure and a structure similar to the ligand binding site of PKC. CR1 is the main site of activated Ras binding to Raf-1 protein kinase. CR2 is present near the amino terminal and contains many serine and threonine residues[55]. CR3, located at the carboxyl terminal, is the catalytic functional domain of Raf-1 protein kinase. The family of Raf kinases is divided into three subtypes: Raf-1, A-Raf and B-Raf. Raf kinases can be activated in the following ways: 1) Raf interacts with Ras on the inside of the cell membrane; 2) dimerization of Raf protein; 3) phosphorylation and dephosphorylation of various sites; 4) separation by Raf kinase inhibitor; 5) binding to Ras kinase inhibitors[48,49]. Raf-1 Ras/Raf/MEK/ERK plays an important role in cell proliferation signal pathway. In the pathway of Ras/Raf/MEK/ERK signal transduction and activation from the Raf cytoplasm to the inside of the cell membrane, Ras is used as an active protein in the upper layer and from two sites, namely the Ras-binding domain and cysteine-rich domain at the N-terminal of Raf-1. Activated Raf-1 continues to activate MEK and MAPK in the lower layer and eventually regulates gene expression by controlling the activity of transcriptional regulatory factors by delivering cell proliferation and differentiation signals to the nucleus[56,57]. Among the subtypes of Raf kinases, A-Raf shows the weak-

est kinase activity, while B-Raf shows the strongest activity. Among the three subtypes, 90% of B-Raf mutations are seen in melanoma[58-60].

After Raf activation, the S-terminal interacts with the catalytic domain MEK (MAPK/ERK kinase, MARK-extracellular regulated kinase) and the catalytic VIII subsystem is phosphorylated in the cool residue and activates MEK. Two subtypes of MEK, MEK1 and MEK2, have molecular weights of 44 and 45 kDa, respectively[24,61]. MEK is a unique and bilaterally specific kinase that activates ERK by phosphorylation of Tyr and Thr regulator sites[50]. The specific phosphorylation activity of MEK Tyr and Thr is of significant physiological importance because ERK occupies a central position in the signalling pathway and any errors in activation can have a profound effect on cellular processes. This two-way recognition and activation mechanism transmits the signal very accurately and prevents errors in ERK activation[62,63]. MEK not only activates ERK, but also establishes ERK in the cytoplasm. When the signal is inactive, ERK is localized in the cytoplasm. After the signal stimulates the phosphorylation and dimerization of ERK, the activated ERKs are transferred to the nucleus, promoting the phosphorylation of cytoplasmic target proteins, or regulating the activity of other protein kinases. Various stimuli such as cytokines, viruses, G-protein-bound receptor ligands and oncogenes play a regulatory role by activating the ERK/MAPK signalling pathway[64,65]. The ERK/MAPK signal pathway can be activated in the following ways: 1) Ca^{2+} channel activation; 2) activation of Ras tyrosine kinase receptors; 3) PKC-mediated activation; 4) activation of receptors bound to G proteins[39,66]. ERK1/2 is located in the cytoplasm in unstimulated cells. Once activated, ERK1/2 passes into the nucleus and regulates the activity of various transcription factors through phosphorylation, thereby regulating cell metabolism and biological functions. Microtubule-associated protein 1 (MAP1) is involved in regulating cell morphology and cytoskeletal redistribution through the phosphorylation of cytoskeletal components such as MAP2 and MAP4. Nuclear transcription factors such as protooncogene c-Fos, protooncogene c-Jun, ETS domain-protective protein Elk-1, protooncogene c-Myc, and cyclic AMP-dependent transcription factor ATF2 are phosphorylated in the nucleus[67,68] (Figure 2). Cytoplasmic ERK1/2 can phosphorylate several other protein kinases in the upper part of the ERK pathway, such as SOS, Raf-1 and MEK, by negative feedback. Activation of ERK/MAPK signal pathways can activate other cellular signalling

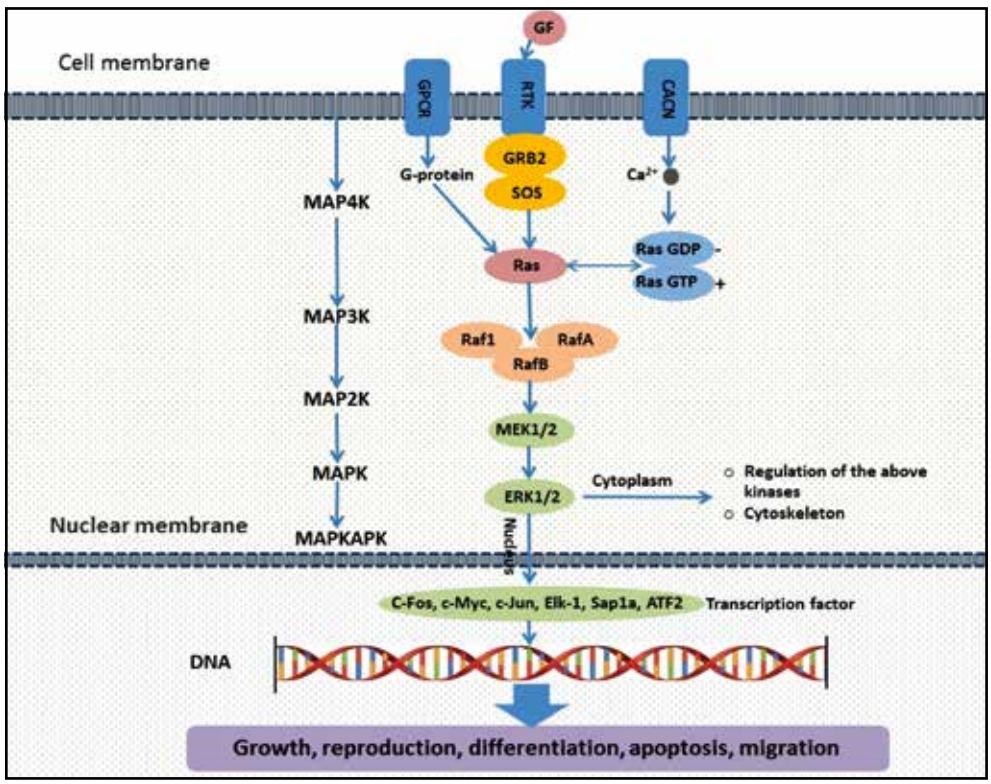

Figure 2. Ras/Raf/MEK/ ERK signal pathway (GF-growth factors; RTK-tyrosine kinase receptors; GRB2 is a protein binding to growth factor receptors 2; SOS - Son of sevenless).

pathways. Vascular endothelial growth factor (VEGF), platelet-derived growth factor and epidermal growth factor (EGF) activate the ERK/MAPK pathway by acting on tyrosine kinase receptors.

When activated, ERK enters the nucleus and binds to transcription factors that cause gene expression in response to extracellular stimuli. It can regulate cell proliferation, differentiation, apoptosis, and transcription[69,70]. According to Rubinfeld Hadara, Seger Rony, the ERK/MAPK signalling pathway is not only involved in the management of biological functions, such as cell proliferation, cell cycle regulation, cell differentiation, cell apoptosis and tissue formation, but is also associated with tumor development. High ERK expression is detected in ovarian, colon, breast and lung cancers[71,72]. ERK/MAPK signal pathway activation may promote the transformation of normal cells into tumor cells and has anti-apoptotic effect, while its inhibition may inhibit the growth of transformed cells[73,74]. Therefore, activation of the ERK/MAPK signalling pathway may be closely associated with tumor emergence and development[75]. Unrestricted cell proliferation, differentiation and lack of apoptosis are important biological features of tumors.

Matrix metalloproteinases (MMPs) are proteolytic enzymes that hydrolyze the extracellular matrix, one of the most important processes in cancer cell invasion and metastasis[76]. Excessive expression of MMPs is beneficial for invasive tumor formation and metastasis, while inhibition of MMR expression has the opposite effect. Activation of the ERK/MAPK signal pathway may enhance tumor invasion and metastasis by regulating MMP expression, whereas inhibition of this signal pathway may reduce tumor invasion and metastasis[76,77]. Cell deformation and migration that occur during tumor metastasis are associated with microfilament-bound protein expression in the cytoskeleton. Studies have shown that hepatocyte growth factor (HGF) enhances migration by activating the ERK/MAPK signalling pathway, thereby promoting invasion and metastasis[69,78]. Blockade of the ERK/MAPK signalling pathway stops tumor invasion and metastasis by inhibiting HGF and other extracellular signals that promote cell movement[69]. In the absence of tumor blood vessels, its tissue rarely exceeds 2 mm^3 [79]. VEGF is an important proangiogenic factor and the most potent provascular endothelial growth cytokine that enhances cancer cell division and vascular construction, increases microvascular permeability and activates endothelial cell migration[69]. ERK/ MAPK signalling pathways may enhance VEGF transcription, increase VEGF expression in tumor cells and activate vascular formation. Interleukin (IL)-8 and VEGF together are manifested in various tumors and may promote tumor angiogenesis, growth and metastasis. ERK1/2 can be used as an alternative pathway causing IL-8 and VEGF expression. Inhibition of the ERK/MAPK signal pathway may be the basis for inhibition of tumor angiogenesis. In addition, hypoxia-inducing VEGF can inhibit apoptosis by activating the ERK/MAPK signalling pathway. The target layer in the lower layer of ERK/MAPK is ribosomal S6 kinase 1 (p70S6K1), an important regulator of cell cycle development and proliferation. Studies show that a vector-based microRNA against p70S6K1 inhibits p70S6K1 activity in ovarian cancer cells and reduces VEGF protein expression[80].

CONCLUSIONS

Through an in-depth analysis of the molecular mechanism of carcinogenesis, it is possible to obtain information about the many biological processes that determine the phenotype of cancer cells. Today, despite the rapid development of medicine, there are difficulties in the systematic detection of fundamental elements in the occurrence of cancer, which creates complications in the early diagnosis and treatment of the disease. In order to penetrate the central block of biological processes occurring in cancer cells, it is necessary to perform an analysis of the pathways leading to it. For example, stable mutations in the genome or defects in the epigenome lead to abnormal cell proliferation, underlying DNA chain damage or dysfunction in the control system, determined by various types of carcinogenic factors, both known and unknown. However, we do not have a fully integrated knowledge of the exact direction of these causal vectors and the complex chemical reactions that take place between them in an interconnected and consistent time sequence. By breaking this chain of reactions, new opportunities can be created in the prevention and treatment of this disease.

It is known that the rate of chemical reactions depends on the concentration and nature of the substances involved in the reaction, the catalysts (enzymes). The high concentration of substrates required for chemical reactions makes cancer cells more reliable than normal cells due to their high-rate plaintiff, active migration and enzymatic potency. Under the influence of these highly concentrated substances and hyperactive catalytic enzymes, the formation of biomolecules of different natures is induced, also activating the chain processes between them. The number of proteins in each segment and the degree of activity of their

catalytic domains are also of great importance in signal transmission along the cell cascade pathways.

The Ras/Raf/MEK/ERK signalling pathway is also a complex network of sequentially activated proteins that play a major role in the onset and development of cancer. Due to the sequential activation of protein kinases in the Ras/Raf/MEK/ERK cascade pathway, the signals are transduced from the plasma membrane along the genome direction and become a potent effector that affects cell activity. Phosphorylation using protein kinases is one of the main biological processes that control the posttranslational modification of proteins, determining cells life. Proteins and molecular factors from other groups are also actively involved in the posttranslational control of proteins synthesized through gene expression and play a role in the complete expression of their function. Due to mutations in the driver genes at the corresponding loci of the chromosome, these processes become overactive and disrupted in cancer cells, resulting in the response to extracellular signals being so intense. While the period from mutation of these genes to the initial clinical stage of cancer is considered an indolent period of carcinogenesis, it leads to reliable protection of cancer cells against the background of de-escalation of the human immune system at the expense of an enormous rate of division.

In the treatment of cancer, it is only through the disintegration or decontamination of elements of this pathogenetic framework that it is possible to maintain healthy cells and to abandon aggressive treatments. Innovative technologies can provide new ways to treat cancer by creating a realistic picture of integrated biological data and ensuring its effective implementation when needed.

Conflict of interest: All authors declare that there are no conflicts of interest.

Contribution of authors: All authors have equally contributed to this work.

Funding statement: None.

REFERENCES

1. Trapeznikov NN, Poddubnaya IV. Handbook of Oncology. Editor Academician of the Russian Academy of Medical Sciences. Moscow: Kappa; 1996.
2. Sanchez-Vega F, Mina M, Armenia J, Chatila WK, Luna A, La KC, et al. Oncogenic signaling pathways in the cancer genome atlas. Cell. 2018;173(2):32137.e10. DOI: 10.1016/j.cell.2018.03.035.
3. Pollard T, Earnshaw W, Lippincott-Schwartz J, Johnson G. Cell biology. 3rd edition. Philadelphia, PA: Elsevier; 2017.
4. Ezkurdia I, Juan D, Rodriguez J M, Frankish A, Diekhans M, Harrow J, et al. Multiple evidence strands suggest that there may be as few as 19,000 human protein-coding genes. Hum Mol Genet. 2014;23(22):5866-78. DOI: 10.1093/hmg/ddu309.
5. Malarkey DE, Hoenerhoff M, Maronpot RR. Carcinogenesis: mechanisms and manifestations. In: Bolon B, Haschek W, Rousseaux C, Ochoa R, Wallig M. Haschek and Rousseaux's handbook of toxicologic pathology. 3rd Edition. Academic Press; 2013, p.107-46.
6. Becnel LB, Ochsner SA, Darlington YF, McOwiti A, Kankanamge WH, Dehart M, et al. Discovering relationships between nuclear receptor signaling pathways, genes, and tissues in Transcriptomine. Sci Signal. 2017;10(476):eaah6275. DOI: 10.1126/scisignal.aah6275.
7. Ochsner SA, Abraham D, Martin K, Ding W, McOwiti A, Kankanamge W, et al. The Signaling Pathways Project, an integrated 'omics knowledgebase for mammalian cellular signaling pathways. Sci Data. 2019;6(1):252. DOI: 10.1038/s41597-019-0193-4.
8. Pecorino L. Molecular biology of cancer: mechanisms, targets, and therapeutics. 3rd edition. Oxford University Press; 2012.
9. Yoo M, Hatfield DL. The cancer stem cell theory: Is it correct? Mol Cells. 2008;26(5):514-6.
10. Reinhardt HC, Yaffe MB. Kinases that control the cell cycle in response to DNA damage: Chk1, Chk2, and MK2. Curr Opin Cell Biol. 2009;21(2):245-55. DOI: 10.1016/j.ceb.2009.01.018.
11. Nigg EA. Mitotic kinases as regulators of cell division and its checkpoints. Nat Rev Mol Cell Biol. 2001;2:21-32.
12. Lim S, Kaldis P. Cdks, cyclins and CKIs: roles beyond cell cycle regulation. Development. 2013;140(15):3079-93. DOI: 10.1242/dev.091744.
13. Gopinathan L, Ratnacaram CK, Kaldis P. Established and novel Cdk/cyclin complexes regulating the cell cycle and development. Results Probl Cell Differ. 2011;53:365-89. DOI: 10.1007/978-3-642-19065-0_16.
14. Kato S, Schwaederle M, Daniels GA, Piccioni D, Kesari S, Bazhenova L, et al. Cyclin-dependent kinase pathway aberrations in diverse malignancies: clinical and molecular characteristics. Cell Cycle. 2015;14(8):1252-9. DOI: 10.1080/15384101.2015.1014149.
15. Foster SS, De S, Johnson LK, Petrini JH, Stracker TH. Cell cycle- and DNA repair pathway-specific effects of apoptosis on tumor suppression. Proc Natl Acad Sci U S A. 2012;109(25):9953-8. DOI: 10.1073/pnas.1120476109.
16. Mazouzi A, Velimezi G, Loizou JI. DNA replication stress: causes, resolution and disease. Exp Cell Res. 2014;329(1):85-93. DOI: 10.1016/j.yexcr.2014.09.030.
17. Visconti R, Della Monica R, Grieco D. Cell cycle checkpoint in cancer: a therapeutically targetable double-edged sword. J Exp Clin Cancer Res. 2016;35(1):153. DOI: 10.1186/s13046-016-0433-9.
18. Rubin SM. Deciphering the retinoblastoma protein phosphorylation code. Trends Biochem Sci. 2013;38(1):12-9. DOI: 10.1016/j.tibs.2012.10.007.
19. DeCaprio JA, Ludlow JW, Lynch D, Furukawa Y, Griffin J, Piwnica-Worms H, et al. The product of the retinoblastoma susceptibility gene has properties of a cell cycle regulatory element. Cell. 1989;58(6):1085-95. DOI: 10.1016/0092-8674(89)90507-2.
20. Pardal R, Molofsky AV, He S, Morrison SJ. Stem cell self-renewal and cancer cell proliferation are regulated by common networks that balance the activation of proto-oncogenes and tumor suppressors. Cold Spring Harb Symp Quant Biol. 2005;70:177-85. DOI: 10.1101/sqb.2005.70.057.
21. Mesplede T, Gagnon D, Bergeron-Labrecque F, Azar I, Senechal H, Coutlee F, et al. p53 degradation activity, expression, and subcellular localization of E6 proteins from 29 human papillomavirus genotypes. J Virol. 2012;86(1):94-107. DOI: 10.1128/JVI.00751-11.
22. El-Deiry WS. p21(WAF1) mediates cell-cycle inhibition, relevant to cancer suppression and therapy. Cancer Res. 2016;76(18):5189-91.

DOI: 10.1158/0008-5472.CAN-16-2055.
23. Otto T, Sicinski P. Cell cycle proteins as promising targets in cancer therapy. Nat Rev Cancer. 2017;17(2):93-115. DOI: 10.1038/nrc.2016.138.
24. Manning G, Whyte DB, Martinez R, Hunter T, Sudarsanam S. The protein kinase complement of the human genome. Science. 2002;298(5600):191234. DOI: 10.1126/science.1075762.
25. Wallace MD, Southard TL, Schimenti KJ, Schimenti JC. Role of DNA damage response pathways in preventing carcinogenesis caused by intrinsic replication stress. Oncogene. 2014;33(28):3688-95. DOI: 10.1038/onc.2013.339.
26. Polatova DS. 413P - The state of molecular biological markers in osteosarcoma. Ann Oncol. 2019;30(Suppl 9):ix138.
27. Malik-Rachline G, Hacohen-Lev-Ran A, Seger R. Nuclear ERK: Mechanism of translocation, substrates, and role in cancer. Int J Mol Sci. 2019;20(5):1194. DOI: 10.3390/ijms20051194.
28. Grimaldi AM, Simeone E, Festino L, Vanella V, Strudel M, Ascierto PA. MEK Inhibitors in the treatment of metastatic melanoma and solid tumors. Am J Clin Dermatol. 2017;18(6):745-54. DOI: 10.1007/s40257-017-0292-y.
29. Bustelo XR. RHO GTPases in cancer: known facts, open questions, and therapeutic challenges. Biochem Soc Trans. 2018;46(3):741-60. DOI: 10.1042/BST20170531.
30. Kidger AM, Sipthorp J, Cook SJ. ERK1/2 inhibitors: New weapons to inhibit the RAS-regulated RAF-MEK1/2-ERK1/2 pathway. Pharmacol Ther. 2018;187:45-60. DOI: 10.1016/j.pharmathera.2018.02.007.
31. Bandaru P, Kondo Y, Kuriyan J. The interdependent activation of sonofsevenless and Ras. Cold Spring Harb Perspect Med. 2019;9(2):a031534. DOI: 10.1101/cshperspect.a031534.
32. Buffet C, Hecale-Perlemoine K, Bricaire L, Dumont F, Baudry C, Tissier F, et al. DUSP5 and DUSP6, two ERK specific phosphatases, are markers of a higher MAPK signaling activation in BRAF mutated thyroid cancers. PLoS ONE. 2017;12(9):e0184861. DOI: 10.1371/journal.pone.0184861. eCollection 2017.
33. Cheng Y. Tian H. Current development status of MEK inhibitors. Molecules. 2017;22(10):1551. DOI: 10.3390/molecules22101551.
34. Eblen ST. Extracellular regulated kinases: Signaling from Ras to ERK substrates to control biological outcomes. Adv Cancer Res. 2018;138:99-142. DOI: 10.1016/bs.acr.2018.02.004.
35. Frodyma D, Neilsen B, Costanzo-Garvey D, Fisher K, Lewis R. Coordinating ERK signaling via the molecular scaffold Kinase Suppressor of Ras. F1000Res. 2017;6:1621. DOI: 10.12688/f1000research.11895. eCollection 2017.
36. García-Gómez R, Bustelo XR, Crespo P. Protein-protein interactions: Emerging oncotargets in the RAS-ERK pathway. Trends Cancer. 2018;4(9):61633. DOI: 10.1016/j,trecan.2018.07.002.
37. Geenen JJJ, Schellens JHM. Molecular pathways: targeting the protein kinase Wee1 in cancer. Clin Cancer Res. 2017;23(16):4540–4. DOI: 10.1158/1078-0432.CCR-17-0520.
38. Lavoie H, Therrien M. Regulation of RAF protein kinases in ERK signalling. Nat Rev Mol Cell Biol. 2015;16(5):281-98. DOI: 10.1038/nrm3979.
39. Lawrence MC, Jivan A, Shao C, Duan L, Goad D, Zaganjor E, et al. The roles of MAPKs in disease. Cell Res. 2008;18(4):43642. DOI: 10.1038/cr.2008.37.
40. Dohlman HG, Campbell SL. Regulation of large and small G proteins by ubiquitination. J Biol Chem. 2019;294(49):1861323. DOI: 10.1074/jbc.REV119.011068.
41. Dummer R, Schadendorf D, Ascierto PA, Arance A, Dutriaux C, Di Giacomo AM, et al. Binimetinib versus dacarbazine in patients with advanced NRAS-mutant melanoma (NEMO): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2017;18(4):435-45. DOI: 10.1016/S1470-2045(17)30180-8.
42. Herrero A, Pinto A, Colon-Bolea P, Casar B, Jones M, Agudo-Ibanez L, et al. Small molecule inhibition of ERK dimerization prevents tumorigenesis by RAS-ERK pathway oncogenes. Cancer Cell. 2015;28(2):170-82. DOI: 10.1016/j.ccell.2015.07.001.
43. Simanshu DK, Nissley DV, McCormick F. RAS proteins and their regulators in human disease. Cell. 2017;170(1):1733. DOI: 10.1016/j.cell.2017.06.009.
44. Guo YJ, Pan WW, Liu SB, Shen ZF, Xu Y, Hu LL. ERK/MAPK signalling pathway and tumorigenesis. Exp Ther Med. 2020;19(3):1997-2007. DOI: 10.3892/etm.2020.8454.
45. Khotskaya YB, Holla VR, Farago AF, Mills Shaw KR, Meric-Bernstam F, Hong DS. Targeting TRK family proteins in cancer. Pharmacol Ther. 2017;173:5866. DOI: 10.1016/j.pharmthera.2017.02.006.
46. Sanchez JN, Wang T, Cohen MS. BRAF and MEK inhibitors: Use and resistance in BRAFmutated cancers. Drugs. 2018;78(5):54966. DOI: 10.1007/s40265-018-0884-8.
47. Plotnikov A, Zehorai E, Procaccia S, Seger R. The MAPK cascades: Signaling components, nuclear roles and mechanisms of nuclear translocation. Biochim Biophys Acta Mol Cell Res. 2011;1813(9):161933. DOI: 10.1016/j.bbamcr.2010.12.012.
48. Roskoski R Jr. ERK1/2 MAP kinases: Structure, function, and regulation. Pharmacol Res. 2012;66(2):10543. DOI: 10.1016/j.phrs.2012.04.005.
49. Roskoski R Jr. Targeting ERK1/2 proteinserine/threonine kinases in human cancers. Pharmacol Res. 2019;142:15168. DOI: 10.1016/j.phrs.2019.01.039.
50. Wainstein E, Seger R. The dynamic subcellular localization of ERK: mechanisms of translocation and role in various organelles. Curr Opin Cell Biol. 2016;39:1520. DOI: 10.1016/j.ceb.2016.01.007.
51. Cassier E, Gallay N, Bourquard T, Claeysen S, Bockaert J, Crepieux P, et al. Phosphorylation of β-arrestin2 at Thr^{383} by MEK underlies β-arrestin-dependent activation of Erk1/2 by GPCRs. Elife. 2017;6:e23777. DOI: 10.7554/eLife.23777.
52. Muñoz-Maldonado C, Zimmer Y, Medová M. A comparative analysis of individual RAS mutations in cancer biology. Front Oncol. 2019;9:1088. DOI: 10.3389/fonc.2019.01088. eCollection 2019.
53. Ma Y, Xu Y, Li L. SPARCL1 suppresses the proliferation and migration of human ovarian cancer cells via the MEK/ERK signaling. Exp Ther Med. 2018;16(4):3195-201. DOI: 10.3892/etm.2018.6575.
54. Mahapatra DK, Asati V, Bharti SK. MEK inhibitors in oncology: a patent review (2015–Present). Expert Opin Ther Pat. 2017;27(8):887-906. DOI: 10.1080/13543776.2017.1339688.
55. Rukhlenko OS, Khorsand F, Krstic A, Rozanc J, Alexopoulos LG, Rauch N, et al. Dissecting RAF inhibitor resistance by structurebased modeling reveals ways to overcome oncogenic RAS signaling. Cell Syst. 2018;7(2):161179.e14. DOI: 10.1016/j.cels.2018.06.002.
56. Holderfield M, Deuker MM, McCormick F, McMahon M. Targeting RAF kinases for cancer therapy: BRAFmutated melanoma and beyond. Nat Rev Cancer. 2014;14(7):45567. DOI: 10.1038/nrc3760.
57. Vandamme D, Herrero A, AlMulla F, Kolch W. Regulation of the MAPK pathway by raf kinase inhibitory protein. Crit Rev Oncog. 2014;19(6):40515. DOI: 10.1615/critrevoncog.2014011922.
58. Colombino M, Capone M, Lissia A, Cossu A, Rubino C, De Giorgi V, et al. BRAF/NRAS mutation frequencies among primary tumors and metastases in patients with melanoma. J Clin Oncol. 2012;30(20):25229. DOI: 10.1200/JCO.2011.41.2452.
59. Dankner M, Rose AAN, Rajkumar S, Siegel PM, Watson IR. Classifying BRAF alterations in cancer: new rational therapeutic strategies for actionable mutations. Oncogene. 2018;37(24):3183-199. DOI: 10.1038/s41388-018-0171-x.

60. Sun W, Kesavan K, Schaefer BC, Garrington TP, Ware M, Johnson NL, et al. MEKK2 associates with the adapter protein Lad/RIBP and regulates the MEK5BMK1/ERK5 pathway. J Biol Chem. 2001;276(7):5093100. DOI: 10.1074/jbc.M003719200.
61. Terrell EM, Morrison DK. Rasmediated activation of the Raf family kinases. Cold Spring Harb Perspect Med. 2019;9(1):a033746. DOI: 10.1101/cshperspect.a033746.
62. Jones JC, Renfro LA, Al-Shamsi HO, Schrock AB, Rankin A, Zhang BY, et al. NonV600 BRAF mutations define a clinically distinct molecular subtype of metastatic colorectal cancer. J Clin Oncol. 2017;35(23):262430. DOI: 10.1200/JCO.2016.71.4394.
63. Seternes OM, Kidger AM, Keyse SM. Dual-specificity MAP kinase phosphatases in health and disease. Biochim Biophys Acta Mol Cell Res. 2019;1866(1):12443. DOI: 10.1016/j.bbamcr.2018.09.002.
64. Wang C, Chen Z, Nie L, Tang M, Feng X, Su D, et al. Extracellular signal-regulated kinases associate with and phosphorylate DHPS to promote cell proliferation. Oncogenesis. 2020;9(9):85. DOI: 10.1038/s41389-020-00271-1.
65. Zhou B, Der CJ, Cox AD. The role of wild type RAS isoforms in cancer. Semin Cell Dev Biol. 2016;58:609. DOI: 10.1016/j.semcdb.2016.07.012.
66. Lu P, Chen J, Yan L, Yang L, Zhang L, Dai J, et al. RasGRF2 promotes migration and invasion of colorectal cancer cells by modulating expression of MMP9 through Src/Akt/ NF-kappaB pathway. Cancer Biol Ther. 2018;20(4):435-43. DOI: 10.1080/15384047.2018.1529117.
67. Krishnamoorthy GP, Davidson NR, Leach SD, Zhao Z, Lowe SW, Lee G, et al. EIF1AX and RAS mutations cooperate to drive thyroid tumorigenesis through ATF4 and c-MYC. Cancer Discovery. 2019;9(2):264-81. DOI: 10.1158/2159-8290.CD-18-0606.
68. Lavoie H, Sahmi M, Maisonneuve P, Marullo SA, Thevakumaran N, Jin T, et al. MEK drives BRAF activation through allosteric control of KSR proteins. Nature. 2018;554:549-53.
69. Song M, Finley SD. Mechanistic insight into activation of MAPK signaling by pro-angiogenic factors. BMC Syst Biol. 2018;12:145. DOI: 10.1186/s12918-018-0668-5.
70. Vladimirova LY. The use of MEK inhibitors in oncology: results and prospects. Success of Modern Natural Science. 2015;3:18-30.
71. Rubinfeld H, Seger R. The ERK cascade: a prototype of MAPK signaling. Mol Biotechnol. 2005;31(2):15174. DOI: 10.1385/MB:31:2:151.
72. Tang Q, Wu J, Zheng F, Hann SS, Chen YQ. Emodin increases expression of insulinlike growth factor binding protein 1 through activation of MEK/ERK/AMPKα and interaction of PPARγ and Sp1 in lung cancer. Cell Physiol Biochem. 2017;41(1):33957. DOI: 10.1159/000456281.
73. Wood LD, Parsons DW, Jones S, Lin J, Sjoblom T, Leary RJ, et al. The genomic landscapes of human breast and colorectal cancers. Science. 2007;318(5853):1108-13. DOI: 10.1126/science.1145720.
74. Yang S, Liu G. Targeting the Ras/Raf/MEK/ERK pathway in hepatocellular carcinoma. Oncol Lett. 2017;13(3):10417. DOI: 10.3892/ol.2017.5557.
75. Mandal R, Becker S, Strebhardt K. Stamping out RAF and MEK1/2 to inhibit the ERK1/2 pathway: an emerging threat to anticancer therapy. Oncogene. 2016;35(20):2547-61. DOI: 10.1038/onc.2015.329.
76. Gialeli C, Theocharis AD, Karamanos NK. Roles of matrix metalloproteinases in cancer progression and their pharmacological targeting. FEBS J. 2011;278(1):16-27. DOI: 10.1111/j.1742-4658.2010.07919.x
77. Braicu C, Buse M, Busuioc C, Drula R, Gulei D, Raduly L, et al. A comprehensive review on MAPK: A promising therapeutic target in cancer. Cancers (Basel). 2019;11(10):1618. DOI: 10.3390/cancers11101618.
78. Caunt CJ, Sale MJ, Smith PD, Cook SJ. MEK1 and MEK2 inhibitors and cancer therapy: the long and winding road. Nat Rev Cancer. 2015;15(10):577-92. DOI: 10.1038/nrc4000.
79. Krishna Priya S, Nagare RP, Sneha VS, Sidhanth C, Bindhya S, Manasa P, Ganesan TS. Tumour angiogenesis-Origin of blood vessels. Int J Cancer. 2016;139(4):729-35. DOI: 10.1002/ijc.30067.
80. Bian CX, Shi Z, Meng Q, Jiang Y, Liu LZ, Jiang BH. P70S6K 1 regulation of angiogenesis through VEGF and HIF-1alpha expression. Biochem Biophys Res Commun. 2010;398(3):395-9. DOI: 10.1016/j.bbrc.2010.06.080.