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Review

The members of the RAS–RAF–MEK–ERK signaling pathway and cancer

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Abstract

Cancer is one of the biggest health problems of contemporary humanity, representing the second cause of death after cardiovascular diseases, caused by many contributing factors, such as population growth, ageing, stress, pollution, unhealthy diet, tumor diversity and heterogeneity, difficulties in correct and early diagnosis and inefficiency of current treatments (e.g. cytoreduction, chemotherapy, radiotherapy, etc.). This leads us to look for new ways of dealing with cancer, such as immunotherapy and personalized therapy, which consider the type of tumour, mutations and expression levels of certain genes, making it necessary to detect specific markers. A category of such specific markers is represented by the proteins involved in inter- and intra-cellular signaling which play essential roles in tumor transformation, progression and dissemination. In cancer, some canonical signaling pathways, including RAS–RAF–MEK–ERK, PI3K–PKB/AKT, JAK–STAT, HIF1–VEGF, TGFβ, NOTCH, RAP1, TP53, β-catenin/WNT, HIPPO, KEAP–NRF2, MYC and CDKN2 (cell cycle), may be dysregulated. In this review, we detail the roles of RAS–RAF–MEK–ERK signaling pathway in tumorigenic processes and the types of abnormalities that affect them in cancer.

Keywords RAS–RAF–MEK–ERK signaling pathway, cancer

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Introduction

The RAS–RAF–MEK–ERK signaling pathway (Figure 1) is a complex intracellular mechanism involved in cell proliferation and differentiation, inflammation, evasion of apoptosis, and support of angiogenesis [1,2]. Transmission of biological signals through the RAS–RAF–MEK–ERK signaling pathway is initiated from outside the cell by binding of numerous cytokines to specific receptors. Such cytokine-receptor pairs involved in the RAS–RAF–MEK–ERK signaling pathway are TGFα and EGF–EGFR/ERBB1/HER1 and ERBB2/HER2, PDGF–PDGFRA and PDGFRB, IGF–IGF1R, FITL–KIT/c-KIT, FLT3L–FLT3, HGF–MET and FGF–FGFR. Receptors activated by ligand binding transmit downstream biological signals through at least four signaling pathways: RAS–RAF–MEK–ERK, PI3K–PKB/AKT, JAK–STAT and PLCγ–PCK. In the RAS–RAF–MEK–ERK signaling pathway, receptors recruit the adaptor protein GRB2 (*Growth factor receptor-bound protein 2*), which plays a pivotal role in signal transduction/cell communication. This protein is well known to bridge the gap between transmembrane receptors and the RAS–RAF–MEK–ERK signaling pathway, its inhibition blocking cell proliferation and transformation and impairing the development of organisms [3,2]. By binding to the SH2- and SH3- domains of the GRB2 adaptor protein, SOS1 *(the human counterpart of Drosophila Son of sevenless 1*), which functions as a RAS-specific guanine nucleotide exchange factor, takes up the signal from it and transmits it directly to members of the *RAS* gene family [4,5,2]. Originally identified in the 1980s as the first isolated human oncogenes, the *RAS* GTP-ase family members *KRAS* (*Kirsten RAS oncogene homolog*) *HRAS* (*Harvey RAS oncogene homolog*) and *NRAS* (*Neuroblastoma RAS oncogene homolog*) constitute the focal point of the RAS–RAF–MEK–ERK signaling pathway, taking up signals from both SOS and PCK, RASGEF and EML4/ALK, and transducing it downstream to RAFs, RALGDS, RASSF1 or PI3K, the latter linking to the PI3K–PKB/AKT signaling pathway [2,6]. In the RAS–RAF–MEK–ERK signaling pathway, members of the RAS family function as mitogen-activated protein kinase kinase kinases (MAPKKK or MAP4K), transducing the biological signal to RAFs. In humans, the *RAF* (*rapidly accelerated fibrosarcoma*) gene family comprises three members, RAF1/c-RAF, BRAF and ARAF, and acts as Mitogen-activated protein kinase kinase kinase (MAPKKK or MAP3K), the first member of a series of three enzymes (the other two being part of the *MEK–Mitogen-activated protein kinase kinase kinase* and *ERK–Extracellular signal-regulated kinase* gene families; Also known as MAP2K or MAPKK, *MEK* gene family com-

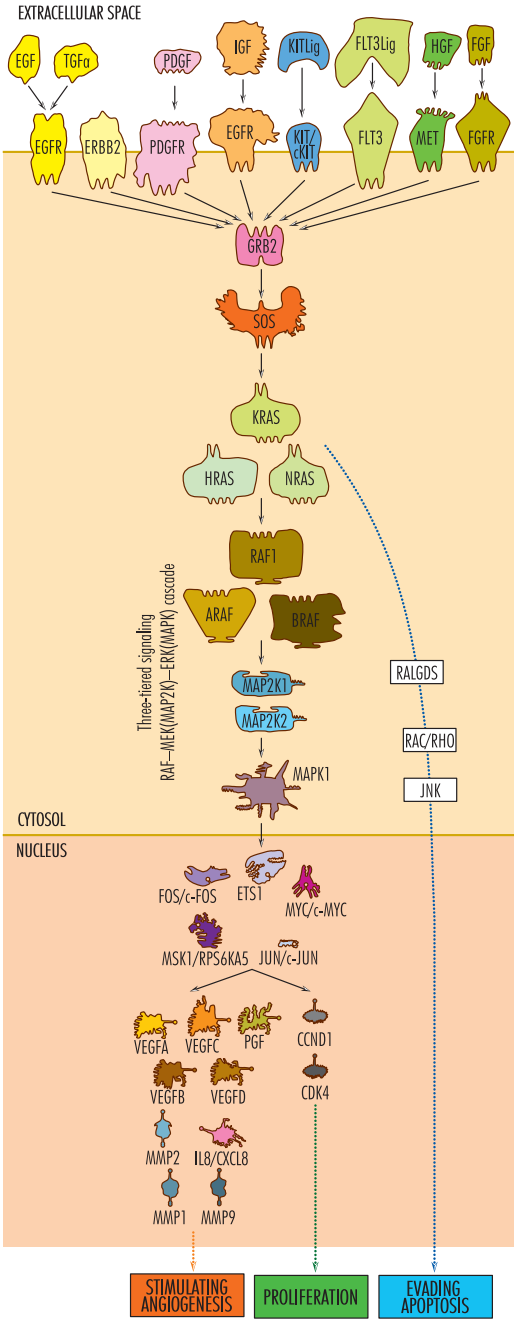

Figure 1. Detail of the signaling pathway RAS–RAF–MEK–ERK in cancer, showing all proteins presented in the text that promote cell proliferation and tumor angiogenesis. On the right, a branch of the RAS–RAF–MEK–ERK signaling pathway, which promotes evasion of apoptosis but whose proteins are not shown in the text, is illustrated.

prises two members, MAP2K1 and MAP2K2, the same as *ERK–Extracellular signal-regulated kinase*, also known as MAPK, with several members, the most important of which are MAPK1 and MAPK3), which constitute the three-tiered RAS-activated RAF–MEK–ERK signaling cascade [7,2]. ERK enzymes act on several nuclear transcription factors, including JUN/c-JUN (*Transcription factor AP-1 subunit Jun*), FOS/c-FOS (*Transcription factor AP-1 subunit Fos*), MYC/c-MYC (*MYC proto-oncogene, BHLH transcription factor*), ETS1 (*ETS proto-oncogene 1, transcription factor*), and MSK1 kinase or RPS6KA5 (*Ribosomal protein S6 kinase A5*). Further, transcription factors stimulate gene expression for the four *vascular endothelial growth factors* (VEGFs), VEGFA, VEGFB, VEGFC and VEGFD, and for PGF (*Placental growth factor*), which stimulates vascular and lymphatic endothelial cell proliferation, and vascular and lymphatic angiogenesis. On the other hand, transcription factors activated by the RAS–RAF–MEK–ERK signaling pathway stimulate the synthesis of members of the *matrix metallopeptidase family* (MMP1, MMP2 and MMP9) and the synthesis of IL8/CXCL8 (*Interleukin 8/C-X-C motif chemokine ligand 8*), promoting cell migration and inflammation, two processes closely associated with tumorigenesis. Moreover, the transcription factors mentioned support *transcription of cyclin D1* (CCND1), overexpressed in cancers, and transcription of *cyclin dependent kinase 4* (CDK4), which, by forming a complex with *cyclin dependent kinase 6* (CDK6), are key players in cell cycle progression, essentially contributing to cell proliferation [2]. Physiologically, the RAS–RAF–MEK–ERK signaling pathway is very active during the embryo-fetal period, when it promotes growth and tissue differentiation of the embryo and fetus, but as these processes slow down, the genes whose products are involved in this signaling pathway become silenced. In the adult stage, their reactivation leads to various diseases, including cancer.

Membrane receptors of the RAS–RAF–MEK–ERK signaling pathway

EGFR/ERBB/HER

Of the four members of the *EGFR/ERBB/HER* gene family, only EGFR/ERBB1/HER1 and ERBB2/HER2 are involved in the RAS–RAF–MEK–ERK signaling pathway, which, after ligand binding (the ligand for ERBB2/HER2 is not known), dimerise, autophosphorylate tyrosine and transmit signals across the transmembrane space to GRB2. The *EGFR/ERBB1* gene is located in the 7p11.2 region and encodes the EGFR/ERBB1 protein of 1210 amino acids and a molecular mass of 134277 Da, which picks up signals from TGFα and EGF ligands and transduces them to the cytosol partner. The *EGFR/ERBB1* gene undergoes abnormalities (e.g. overexpression, activating mutations) in a wide variety of cancers, including oral, esophageal, bladder, cervical, breast, laryngeal, salivary glands, oropharyngeal, pancreatic and appendix cancers, and non-small cell lung carcinoma, choriocarcinoma and glioma [8,9,10,2,11,12,13]. Modern medicine has introduced a number of products directed against EGFR/ERBB1/HER1 into cancer treatment regimens, approved after 2000, including tyrosine kinase inhibitors (Gefitinib, Erlotinib, Afatinib, Dacomitinib, Osimertinib and Vandetanib) and monoclonal antibodies (Cetuximab, Panitumumab, Necitumumab), although for some of these, tumour cells develop resistance. The *HER2/ERBB2* gene has no known ligand, but this does not mean that it cannot exist. It is located in 17q12 and encodes HER2/ERBB2 protein (1255 amino acids; 137910 Da), but by forming a dimer with HER3/ERBB3, it forms a very potent complex [14,15]. Abnormalities in *HER2/ERBB2* gene function occur in a variety of cancers, including gastric, pancreatic, bladder, endometrial, ovarian, cervical, breast, salivary glands, fallopian tubes, pancreatic and appendix cancers, as well as in choriocarcinoma, glioma and cholangiocarcinoma. Treatment regimens for some cancers, which target HER2/ERBB2, include the tyrosine kinase inhibitors Lapatinib, Neratinib and Tucatinib, and monoclonal antibodies or antibody drug conjugates Trastuzumab, Pertuzumab, Trastuzumab emtansine, Trastuzumab deruxtecan, Panitumumab and Margetuximab [16,17;9,18,10,2,20,11,19,13].

PDGFR

The *PDGFR* (platelet derived growth factor receptors) gene family comprises three members, *PDGFRA*, *PDGFRB* and *PDGFRC*, of which only the first two function in the RAS–RAF–MEK–ERK signaling pathway, which, after interaction with PDGF, form a homodimer (by binding PDGFB or PDGFD) or a heterodimer (by binding PDGFA and PDGFB). The *PDGFRA* gene is located in 4q12 and encodes the PDGFRA protein, with chain length of 1089 amino acids and molecular mass of 122670 Da. It undergoes abnormalities (e.g. mutations P130S, W349C, V469A, V536E, F808L, D842V, N870S, G829R, E996K, D1071N, S1049CH) in numerous cancers, including glioma, glioblastoma, lung adenocarcinoma, colon adenocarcinoma, cutaneous melanoma, chronic eosinophilic leukemia, and gastrointestinal stromal tumor [21,22,2,23], and is targeted by Imatinib, Sunitinib, Ripretinib, Avapritinib drugs [24]. The *PDGFRB* gene is located in 5q32 and encodes the PDGFRB protein, with size of 1106 amino acids and molecular mass

of 123968 Da. It is mutated in lung and colon adenocarcinoma, cutaneous melanoma, breast invasive ductal carcinoma, glioma, and melanoma [25,26], being targeted by Sunitinib and Regorafenib drugs [24].

IGF1R

The *IGF1R* gene is located in 15q26.3 and encodes the IGF1R protein, with a size of 1367 amino acids and molecular mass of 154793 Da, which has tyrosine kinase activity and binds insulin-like growth factor with high affinity. Abnormalities of this gene (e.g., missense, nonsense and silent mutations, frameshift, and in-frame deletions) are found in several cancers, including hepatocellular and breast invasive ductal carcinoma, lung, colon, and endometrial endometrioid adenocarcinoma, malignant pleural mesothelioma, synovial sarcoma and cutaneous melanoma [27,2,28]. Among the inhibitors targeting IGF1R in cancer and other conditions are Zykadia, approved in 2014, Tepezza, approved in 2020, and Xentuzumab, Ganitumab, AXL1717, IGF-MTX, W0101 and FPI-1434, which are in clinical trials [29].

KIT/cKIT

KIT/c-KIT gene is located in the 4q12 region and encodes for the tyrosine kinase transmembrane receptor KIT/cKIT (*V-Kit Hardy-Zuckerman 4 Feline Sarcoma Viral Oncogene-Like Protein*), with a size of 976 amino acids and a molecular mass of 109865 Da. KIT/c-KIT is altered in several cancers, including gastrointestinal stromal and appendiceal tumors, lung and colon adenocarcinoma, conventional glioblastoma multiforme, and melanoma [30,18; 2; GeneCards, 2022; 13) and is inhibited by Imatinib, Sunitinib, Regorafenib, Ripretinib, Avapritinib. The V654A mutation confer resistance to Imatinib [24,32].

FLT3

The *FLT3* gene is located in 13q12.2 and encodes the Fms-related tyrosine kinase 3 receptor, FLT3, with a size of 993 amino acids and a molecular mass of 112903 Da, whose ligand binding induces plasma membrane homodimer formation and FLT3 autophosphorylation. FLT3 protein is abnormal in acute myeloid leukemia, colon and lung adenocarcinoma, cutaneous melanoma and invasive ductal carcinoma of the breast [33,18,2]. FLT3 inhibitors are classified as first-generation, type 1 inhibitors (Midostaurin, Lestaurtinib, Sunitinib), first-generation, type 2 inhibitors (Sorafenib, Pexidartinib, Ponatinib), second-generation, type 1 inhibitors (Gilteritinib, Crenolanib, MRX-2843) and second-generation, type 2 inhibitors (Quizartinib) (20,35].

MET

MET – MNNG HOS transforming gene is located in 7q31.2 and encodes MET protein, with size of 1390 amino acids and molecular mass of 155541 Da, a member of the class IV receptor tyrosine kinase family, which, by interacting with hepatocyte growth factor (HGF), dimerizes and becoming active, interacts with the GRB2 carcinoma protein. Somatic MET mutations, such as D1228N, Y1235D, and M1250T and/or amplifications are reported in several cancers, including lung, gastric, esophageal, colorectal, clear cell ovarian and appendix cancers, as well as in gliomas, renal cell carcinomas, hepatocellular carcinomas and head and neck squamous cell carcinoma [36,37,18,2,13]. MET inhibitors in use (Osimertinib, a third-generation drug) or in various phases of clinical testing (multi-target tyrosine kinase inhibitors – Crizotinib, Cabozantinib, Foretinib, Glesatinib and Merestinib, selective MET tyrosine kinase inhibitors – Tepotinib, Savolitinib, Capmatinib, Tivantinib and SAR125844, and anti-MET antibodies – Onartuzumab, Telisotuzumab and JNJ-61186372) are predominantly for non-small cell lung cancer [38,39].

FGFR

The *FGFR* – fibroblast growth factor receptor gene family comprises four members, *FGFR1*, *FGFR2*, *FGFR3* and *FGFR4*, which encode proteins involved in the transduction of the biological signal from FGF in the extracellular space to different molecules in the cytoplasmic space. The *FGFR1* gene is located in 8p11.23 and encodes the FGFR1 protein, with a size of 822 amino acids and a molecular mass of 91868 Da. Mutations of the *FGFR1* gene are activating or can amplify the expression of its product and are identified in a large number of cancers, including breast, ovarian, bladder, prostate and lung cancers, oral squamous cell, esophageal squamous cell carcinomas, colon and appendix adenocarcinomas. The *FGFR2* gene is located in 10q26.13 and encodes FGFR2 protein, with a size of 821 amino acids and a molecular mass of 92025 Da. Abnormalities, such as mutations, amplifications or translocations, activate the *FGFR2* gene and are identified in breast, endometrial and gastric cancers, as well as in cutaneous melanoma, colon adenocarcinoma, appendix and lung adenocarcinoma. The *FGFR3* gene is located in 4p16.3 and encodes the FGFR3 protein, with a size of 806 amino acids and a molecular mass of 87710 Da. Activating abnormalities of the *FGFR3* gene are reported in a wide variety of cancers, including urothelial, bladder, breast, head and neck, lung, brain, gastric, pancreatic, colorectal, kidney, endometrial, ovarian, appendiceal, and cervical cancers. The fourth member of the family is the *FGFR4* gene, located in 5q35.2, which encodes the FGFR3 protein, with a size of 802 amino acids and a molecular mass of 87954 Da. It undergoes missense, nonsense, and silent mutations, and frameshift insertions and

deletions, in lung adenocarcinoma, colon adenocarcinoma, breast invasive ductal carcinoma, cutaneous melanoma, and endometrial endometrioid adenocarcinoma [40–47,18,2]. Among their inhibitors are Pemigatinib, Erdafitinib, Infigratinib, Derazantinib, Futibatinib [48].

Cytoplasmic proteins of the RAS–RAF–MEK–ERK signaling pathway

GRB2

By interacting with the cytoplasmic domains of transmembrane receptors, GRB2 protein is activated, constitutes the first effector of the RAS–RAF–MEK–ERK signaling pathway in the cytoplasm and allows downstream binding of SOS1 protein to its SH2- and SH3- domains, the latter complexing the proline-rich regions of other proteins. The GRB2 protein is 217 amino acids in size and has a molecular mass of 25206 Da and is encoded by the *GRB2* gene in the 17q25.1 region. It appears not to be mutated in cancer, but only to fuse with the RET proto-oncogene in some cases of pheochromocytoma [49,50,2,51].

SOS1

The SOS1 protein, 1333 amino acids in size, with a molecular mass of 152464 Da and encoded by the *SOS1* gene, located in band 2p22.1, binds the SH2- and SH3- domains of its partner in the RAS-RAF-MEK-ERK pathway, GRB2. Further, SOS1 functions as a guanine nucleotide exchange factor for RAS proteins and is regarded as the pacemaker of KRAS. Nucleotide sequence alteration of the SOS1 gene, such as the N233Y point mutation, is very rarely reported in a small number of cases of lung, colon, and endometrial endometrioid adenocarcinoma, cutaneous melanoma, and breast invasive ductal carcinoma [52,53,2]. Having an important function in activating the RAS family member-mediated signaling pathway, SOS1 is targeted by several inhibitors in clinical trials, including Afatinib, Olmutinib, Erlotinib, Refametinib, Trametinib, Nintedanib, Paclitaxel, Abemaciclib, Gemcitabine, BAY293, SAH-SOS1 and BI1701963 [54,55,20].

RAS

The *RAS* gene family comprises three members, *KRAS*, *HRAS* and *NRAS*, which encode central proteins of the RAS–RAF–MEK–ERK signaling pathway. They are activated by SOS1, RASGEF, EML4/ALK, RET/PTK, TRK and PCK proteins and transmit biological signals via four downstream partners: RAF, in the RAS–RAF–MEK–ERK signaling pathway, through which it stimulates cell proliferation and angiogenesis, RASSF1, involved in cell proliferation and apoptosis evasion, PI3K, through which it activates the PI3K–PKB/AKT signaling pathway, involved in angiogenesis and apoptosis evasion, and RALGDS, which takes cells out of the programmed cell death program [2]. Of the three members, *KRAS*, located in the 12p12 region. 1 and encoding the KRAS protein, with a size of 189 amino acids and molecular mass of 21656 Da, undergoes the most activating mutations in numerous cancers [56], especially in gastrointestinal cancers [57], including numerous types of appendiceal cancers [58], pancreatic, colon, colorectal and rectal adenocarcinomas, and lung adenocarcinomas [59]. Other family members are less prone to mutations, probably due to their less important function in cancer signaling pathways. Thus, the *HRAS* gene, located in the 11p15.5 region and encoding the HRAS protein, with a size of 189 amino acids and a molecular mass of 21298 Da, is mutated in several tumor types, such as melanomas, follicular thyroid, bladder, and appendiceal cancers, and oral squamous cell carcinomas [60,13], whereas the *NRAS* gene (1p13. 2), which encodes the NRAS protein, with a size of 189 amino acids and a molecular mass of 21229 Da, is rarely mutated in cancers, these being reported in rectal somatic and follicular thyroid cancers and juvenile myelomonocytic leukemia, but also in a small number of appendiceal cancers [61,13]. Among the many RAS family protein inhibitors are: Tipifarnib, Lonafarnib (farnesyl transferase inhibitors), Sotorasib (AMG-510), MRTX849, MTRX1133, JNJ-74699157, GDC-6036, LY3499446, tergeting KRAS harboring G12C mutation, D-1553, ARS-1620, AMG 404, Trametinib, RMC-4630, Afatinib, Pembro, Panitumumab, Carbo/pem/docetaxel, Everolimus, Palbociclib, Bevacizumab, Adagrasib, TNO155, LY3537982, Abemaciclib, Erlotinib, Sintilimab, Temuterkib, LY3295668, Cetuximab, Atezo, Cetuximab, Bevacizumab, Erlotinib, D-1553, JDQ443, TNO155, Spartalizumab, TNO155, EGF816, RMC-4630, Cobimetinib/osimertinib, BI 1701963, BI 3,011,441, Irinotecan, directed against KRAS and many in various phases of clinical testing [62], Tipifarnib and Salirasib targeting HRAS [63,64], but there are encouraging results on the ability of some MEK (Trametinib) and BRAF (Dabrafenib) inhibitors to inhibit, together or in other combinations, HRAS [65], Trametinib, Binimetinib, Pimasertib, RO4987655 (MEK inhibitor), Alpelisib+binimetinib, GSK2141795 (AKT inhibitor)+Trametinib, Ribociclib+binimetinib, Sorafenib+tivatinib, Axitinib+carboplatin/paclitaxel, and Ulixertinib, used as NRAS inhibitors in various tumor types [66].

RAF

The *RAF* gene family comprises three members, *RAF1*, *ARAF* and *BRAF*, whose products receive signals from two

directions, RAS proteins and PRK proteins, and serve as the first members of the RAF–MEK–ERK three kinase signaling cascade, after which signals are transmitted within the nucleus [2]. The *RAF1* gene is located in chromosomal band 3p25.2, encodes the RAF1 protein, with size of 648 amino acids and molecular mass of 73052 Da, and undergoes fusions, rearrangements, missense mutations, nonsense mutations, and silent mutations in bladder urothelial carcinoma, long adenocarcinoma, endometrial endometrioid adenocarcinoma, colon adenocarcinoma, cutaneous melanoma, and stomach cancers [67–70]. The *ARAF* gene is located in the Xp11 region. 3, encodes the ARAF protein, with size of 606 amino acids and molecular mass of 67585 Da, and is mutated in several cancers, including lung, colon, endometrial endometrioid, and high-grade ovarian serous adenocarcinoma, gallbladder cancers, and breast invasive ductal carcinoma, its mutations being correlated with malignant phenotypes in some cancers, including gallbladder cancer types, or with resistance to some chemotherapeutics [71–73]. The *BRAF* gene is located in the 7q34 region, encodes the serine/threonine kinase BRAF, with a size of 766 amino acids and molecular mass of 84437 Da, and undergoes mutations, most commonly V600E, in several cancers, including non-Hodgkin lymphoma, colorectal and appendiceal cancers, thyroid carcinoma, non-small cell lung carcinoma, hairy cell leukemia and adenocarcinoma of lung [75,76,13]. Several molecules, including LXH254, directed against ARAF [77], Dabrafenib and Vemurafenib, directed against BRAF [65,20], are used in the treatment of cancers which harbor mutations in RAF family genes.

MAP2K/MEK

The *MAP2K* gene family comprises several members, of which, in cancer, only *MAP2K1* and *MAP2K2* are involved in the RAS–RAF–MEK–ERK signaling pathway, as ordinal two protein kinases in the cascade of three such proteins. The *MAP2K1* gene is located in region 15q22.31 and encodes the MAP2K1 protein, with size of 393 amino acids and molecular mass of 43439 Da. Its mutations occur in cutaneous melanoma, lung, and colon adenocarcinoma, colorectal cancers, melanoma, and breast invasive ductal carcinoma [78,79]. In colorectal cancers, mutations in this gene cause poor response to treatment with anti-EGFR compounds [80]. The *MAP2K2* gene is located in band 19p13. 3, encodes the MAP2K2 protein, with size of 400 amino acids and molecular mass of 44424 Da, mutated in several types of carcinomas, including breast invasive ductal carcinoma, cutaneous melanomas and adenocarcinomas, including colon, lung, and high-grade ovarian serous adenocarcinoma [81,82]. Among MEK inhibitors, are used/will be used Alectinib+cobimetinib, Atezolizumab+cobimetinib, AZD8330 (ARRY-424704), Binimetinib, Binimetinib+erlotinib/+encorafenib±ribociclib/+carboplatin or pemetrexed/+Palbociclib/+pembrolizumab, Brigatinib+binimetinib, Carboplatin+pemetrexed+binimetinib, Cisplatin+pemetrexed+binimetinib, Cobimetinib, Cobimetinib+alectinib/+atezolizumab/+vemurafenib, CS-3006, Durvalumab+selumetinib+tremelimumab, E6201, EGF816+trametinib, Encorafenib+binimetinib+docetaxel, FCN-159, GDC-0623, HL-085, HL-085+docetaxel, MEK162, Mirdametinib, PD-0325901, PD-0325901+palbociclib/+dacomitinib, Pimasertib, Refametinib, RO4987655, RO5126766, Selumetinib, Selumetinib+docetaxel/+erlotinib/+vandetanib/+afatinib/+gefitinib/+durvalumab/+paclitaxel/+osimertinib/+durvalumab+tremelimumab/+vandetanib, SHR7390, TAK-733m, TQ-B3234, Trametinib, Trametinib+dabrafenib/+docetaxel/+pemetrexed/+ceritinib/+dabrafenib/+navitoclax/+lapatinib/+pembrolizumab, Trametinib+carboplatin+paclitaxel+radiation therapy, WX-554, some of them still being in various phases of clinical testing, and others are expected to inhibit MEK proteins when there are also mutations in the KRAS, EGFR or BRAF V600E genes [83–85,65,66,86,87].

ERK/MAPK1

The *ERK/MAPK1* gene is located in the 22q11.22 region and encodes the ERK/MAPK1 protein, 360 amino acids in size and molecular mass of 41390 Da, and the third member of the three-protein kinase cascade of the RAS–RAF–MEK–ERK signaling pathway. Activated by MEK/MAP2K proteins, the ERK/MAPK1 protein crosses the nuclear membrane, where it activates several proteins that act as activators of transcription factors [2]. Missense, nonsense, and silent mutations of the *ERK/MAPK1* gene are reported in cervical, and skin cancer, lung, colon, and endometrial endometrioid adenocarcinoma, bladder urothelial, and breast invasive ductal carcinoma [88,89]. ERK/MAPK1 targeting is sometimes seen as the Achilles heel of the RAS–RAF–MEK–ERK signaling pathway, and a number of molecules designed to inhibit ERK/MAPK1 have been clinically tested, including FRI-20, ON-01060, VTX-11e, 25-OH-D3-3--BE, B3CD, Bromoacetoxycalcidiol, FR-180204, AEZ-131, AEZS-131, AEZS-136, SCH-772984, AZ-13767370, BL-EI-001, LY-3214996, LTT-462, KO-947, CC-90003, GDC-0994, RG-7842, MK-8353, SCH900353, BVD-523, and Ulixertinib [90,20].

Nuclear proteins of the RAS–RAF–MEK–ERK signaling pathway

The nuclear proteins of the RAS–RAF–MEK–ERK signaling pathway are grouped in a two-step cascade, where

the first step is activated by the ERK/MAPK1 protein (JUN/c-JUN, FOS/c-FOS, MYC/c-MYC, ETS1 and MSK1/RPS6KA5), and the second, which includes VEGFA, VEGFB, VEGFC, VEGFD, PGF, MMP1, MMP2, MMP9 and IL8/CXCL8 proteins involved in angiogenesis, and CCND1 and CDK4 proteins involved in proliferation, is activated by the first step proteins.

JUN/c-JUN

The *JUN/c-JUN* gene is located in the 1p32 region. 1 and encodes the JUN/c-JUN protein, 331 amino acids in size and with a molecular mass of 35676 Da, a nuclear component of the transcription factor activator protein 1 (AP-1), together with members of the *FOS* gene family (*c-FOS*, *FOSB* and the smaller splice variants FRA1 and FRA2), involved in transcription activation at the TRE/AP-1 element level, and also a key regulator of mitochondrial glutaminase (GLS) levels in cells [91,92,2]. Nucleotide sequence alteration of the JUN/c-JUN gene, through missense, nonsense and silent mutations, as well as frameshift insertions and deletions, is reported in cancers of the gastrointestinal, including colon adenocarcinoma, lung, including lung adenocarcinoma, reproductive, including adenocarcinoma of the prostate and invasive ductal carcinoma of the breast, the latter being associated with cell proliferation and tumour angiogenesis, as well as in skin cancers, including skin cancer, or cancers of fatty tissue, such as dedifferentiated liposarcoma [91,93,94]. Numerous molecules with the property of inhibiting c-JNK (c-Jun N-terminal kinases) are currently being tested, of which JNK-IN-8 shows specificity for JUN/c-JUN [95,96].

FOS/c-FOS

The *FOS/c-FOS* gene is located in the 14q24.3 region and encodes the FOS/c-FOS protein, with a size of 380 amino acids and a molecular mass of 40695 Da. It heterodimerizes with the JUN/c-JUN protein and forms transcription factor activator protein 1 (AP-1), which binds and activates the transcription of TRE/AP-1 elements, involved in the regulation of expression of numerous genes whose transcription products are involved in a wide variety of biological processes, including differentiation, proliferation, and apoptosis [97,2,98]. Activating mutations of the FOS/c-FOS gene are reported in several cancers, including osteosarcomas, endometrial, cervical and thyroid carcinomas, head and neck, and oral squamous cell carcinoma, breast and ovarian cancers, mesotheliomas, lung, colorectal, esophageal and skin cancers, and melanomas [97,99,100]. Of the FOS/c-FOS inhibitors, the best known is T-5224, which is in trials and, at a preclinical level, inhibits some inflammatory diseases, including arthritis [101].

MYC/c-MYC

The *MYC/c-MYC* gene is located in the 8q24.21 region and encodes the MYC/c-MYC protein, 439 amino acids in size and 48804 Da molecular mass, which, through heterodimerization with MAX, folds and becomes transcriptionally active, binding specifically to the consensus DNA sequence CANNTG, which is an Enhancer-box [2,102,103]. The *MYC/c-MYC* gene is aberrantly expressed in approximately 50-70% of human cancers, including invasive ductal breast carcinoma and invasive breast carcinoma, adenocarcinoma of the lung, colon and prostate, as well as endometrial, hematopoietic, lymphoid and stomach cancers [104–107]. Over time, numerous molecules have been developed that target MYC/c-MYC activity, including QN-1, APTO-253, AZD5153, GSK525762 and dBET1, which target *MYC* gene transcription, MLN0128, Silvestrol, eFT226 and BTYNB, which target MYC mRNA translation, [1,2,3] triazolo [4,5-d] pyrimidine derivatives, SZL-P1–41, TD19 and Volasertib, which affect MYC protein stability, MYCMI-6, KI-MS2-008, Omomyc, SaJM589, KJ-Pyr-9 and FPPa-OmoMYC, which target MYC–MAX heterodimer, Sulfopin, ASH2L-derived peptides and C620-0696, which impair accessibility of MYC protein to downstream genes, and B-I09, 8866, Purvalanol A, Berbamine, VX-680 (MK-0457), AZD1152, AZD7648 and Dinaciclib, candidate drugs for alternative selective killing of the dysregulated cells through synthetic lethality conferred by *MYC* overexpression, many of them still being in various phases of preclinical/clinical testing [107–109].

ETS1

The *ETS1* gene is part of a 28-member gene family in humans, located in the 11q24.3 region and encodes the ETS1 protein, 441 amino acids in size and molecular mass of 50408 Da, and, depending on the biological context, acts as an oncogene or a tumour suppressor gene. ETS1 gene aberrations, including fusions, missense, nonsense and silent mutations, as well as frameshift deletions, are associated with endometrial, bowel (colon adenocarcinoma), pleural cancers, but also melanoma, anaplastic oligodendroglioma and basal cell carcinoma [110–112,2,113]. Inhibition of ETS1 activity is pursued through the use of inhibitors of its effectors, in the case of the RAS–RAF–MEK–ERK signaling pathway the use of the MEK inhibitor, Trametinib [114], is proposed, as well as through the use of molecules that target the full range of ETS family members, such as YK-4-279 [115].

MSK1/RPS6KA5

The MSK1/RPS56KA5 gene is located in 14q32.11 and encodes the MSK1/RPS56KA5 protein, with a size of 802 amino acids and molecular mass of 89865 Da, located in the cytoplasm and nucleoplasm and involved in histone-serine

phosphorylation, regulation of histone modification, and regulation of transcription. It is expressed in a wide variety of tissues and, in the RAS–RAF–MEK–ERK signaling pathway, activates the MYC/c-MYC protein [2,116]. MSK1 overexpression is associated with a better survival rate in breast cancer [117] but with increased proliferation and metastasis in uveal melanoma [118].

*VEGF*s

Members of the *VEGF* gene family are directly involved in angiogenesis and lymphangiogenesis by stimulating endothelial cell proliferation, budding and vascular remodeling, processes that lead to the formation of new blood or lymph vessels from pre-existing ones. It is well known that members of this family are some of the most potential angiogenic factors. The *VEGF* gene family comprises four members, *VEGFA*, *VEGFB*, *VEGFC* and *VEGFD/FIGF*, which, in addition to proteins in the RAS–RAF–MEK–ERK signaling pathway, are also activated by HIF1A, as the first molecule synthesized by cells undergoing hypoxia [2]. The *VEGFA* gene is located in 6p21.1 and encodes the VEGFA protein, with size of 232 amino acids, and a molecular mass of 27042 Da. Aberrations of this gene, including missense, nonsense, and silent mutations, and frameshift insertions are present in cancers of the gastrointestinal (esophageal and colon adenocarcinoma), reproductive (endometrial cancer and breast invasive ductal carcinoma), skin cancers, lung adenocarcinomas, and osteosarcomas. The *VEGFB* gene is located in 11q13. 1, encodes VEGFB protein, with size of 207 amino acids, and a molecular mass of 21602 Da, and is rarely mutated, predominantly in adenosquamous lung carcinoma and endometrial endometrioid adenocarcinoma. The *VEGFC* gene is located in 4q34. 3 and encodes the VEGFC protein, with size of 419 amino acids, and a molecular mass of 46883 Da, and is rarely mutated in cancer. The *VEGFD/FIGF* gene is located in Xp22.2 and encodes the VEGFD/FIGF protein, with size of 354 amino acids, and a molecular mass of 40444 Da. Mutations of this gene occur rarely in cancer [119–126].

PGF

The *PGF* gene is located in cytogenetic band 14q24.3 and encodes the PGF protein, with size 221 amino acids and molecular mass of 24789 Da [127]. Abnormalities in PGF gene expression occur in numerous cancers, in renal and liver cancers it is correlated with poor prognosis, and in intrahepatic cholangiocarcinoma, the PGF gene is overexpressed [128]. Promoting angiogenesis, an essential process in tumour development, VEGFs and PGF have long been targeted, against which numerous chemical compounds have been developed, including Apatinib, Bevacizumab, Cabozantinib, Pazopanib, Ramucirumab, Sorafenib, Sunitinib, Vandetanib, Zif-Aflibercept and the mAb 33C3. Although they inhibited the formation of new blood vessels or lymph vessels from pre-existing ones, they had side effects worth considering. Thus, hypertension, artery clots, and slowed or stopped wound healing were common, and less commonly, gastrointestinal perforation and fistula formation. Currently, several therapeutic combinations are being evaluated in solid tumours based on immune-checkpoint inhibitors (ICIs) in combination with anti-angiogenic agents, including ipilimumab+bevacizumab, atezolizumab+bevacizumab, avelumab+axitinib, pembrolizumab+axitinib, cabozantinib+nivolumab+ipilimumab, axitinib+avelumab, atezolizumab+bevacizumab, regorafenib+nivolumab, sintilimab+bevacizumab, atezolizumab+bevacizumab+paclitaxel, nivolumab+axitinib, atezolizumab+RFA+bevacizumab+atezolizumab, and bevacizumab+atezolizumab+paclitaxel [129,130].

*MMP*s

The *MMP* gene family encodes zinc-dependent endopeptidases and the most important proteases involved in extracellular matrix remodeling, with *MMP1*, *MMP2* and *MMP9* involved in the RAS–RAF–MEK–ERK signaling pathway. The *MMP1* gene is located in the 11q22.2 region and encodes the MMP1 protein, 469 amino acids in size and 54007 Da molecular mass, which cleaves type I, II and III collagens. The *MMP2* gene is located in the 16q12 band. 2 and encodes the MMP2 protein, with a size of 660 amino acids and a molecular mass of 73882 Da, which cleaves denatured type IV and V collagen and elastin. The *MMP9* gene is located in the 20q13.12 region and encodes the MMP9 protein, with a size of 707 amino acids and a molecular mass of 78458 Da, which cleaves type IV and V collagens [2,131–133]. Matrix metalloproteinase inhibitors indicated to be used in cancer include Marimastat, Prinomastat, Tanomastat and Neovastat [134], Marimastat being proposed to be used in combination with a cytotoxic agent and delivered via lysolipid-containing thermosensitive liposomes, for the inhibition of tumor metastasis [135].

IL8/CXCL8

The *IL8/CXCL8* gene is located in band 4q13.3 and encodes the CXCL8 protein, with a size of 99 amino acids and molecular mass of 11098 Da, one of the main factors stimulating the inflammatory response, being synthesized by mononuclear macrophages, neutrophils, eosinophils, T lymphocytes, epithelial cells, and fibroblasts. In cancer, IL8/CXCL8 influences the tumor microenvironment, promotes transformed cell survival, stimulates tumor progression, epithelial-to-mesenchymal transition and angiogenesis, and inhibits anti-tumor immune effectors. Aberrations of the *IL8/*

CXCL8 gene, including mutations, amplifications, deletions and copy number amplification of the mRNA are identified in numerous cancers, such as non-small cell lung cancer, colorectal cancer, head and neck cancer, cervical cancer, ovarian cancer, uterine endometrioid carcinoma, breast cancer, pancreatic cancer, lung cancer, endometrial cancer, mature B-cell lymphoma, bladder cancer, esophagogastric cancer, bone cancer, melanomas, hepatobiliary cancer and thyroid cancer [2,136,137].

CCND1

The *CCND1* gene is located in the 11q13.3 region and encodes cyclin D1, with a size of 295 amino acids and molecular mass of 33729 Da. Part of the cyclin family, CCND1 regulates CDK kinase activity. In the RAS–RAF–MEK–ERK signaling pathway, CCND1 and cyclin dependent kinase 4 (CDK4) promote tumor progression by stimulating cell proliferation [2]. Aberrations in *CCD1* gene function, such as mutations, amplification and overexpression, are common in numerous types of human tumors, including endometrial, bowel, stomach non-small-cell lung, endometrial, pancreatic, breast, and colorectal cancers, breast invasive ductal, breast invasive lobular and breast invasive carcinoma, bladder urothelial, and head and neck squamous cell carcinoma, melanoma, and endometrial endometrioid adenocarcinoma [138–140].

CDK4

The *CDK4* gene is located in the 12q14.1 region and encodes cyclin dependent kinase 4, with a size of 303 amino acids and molecular mass of 33730 Da. Together with its partner, CDK6, CDK4 plays a very important role in cell cycle progression from G1 to S phase and in RB1 protein activation, and aberrations in the function of this gene, including missense and silent mutations, are reported in numerous cancers, including long adenocarcinoma, well differentiated/dedifferentiated liposarcomas, conventional glioblastoma multiforme, glioblastoma, endometrial, intestinal, and skin cancers adenocarcinoma [141,142], in which it promotes cellular proliferation and tumor progression (2). Among the second-generation inhibitors tested against CDK4 and other CDKs are: BAY1000394, P1446-05, PD0332991, R547, RGB-286638, ZK304709 [138], and in breast cancer, against CCND1-CDK4-CDK6 complex formation, the combinations Palbociclib+letrozole, Palbociclib+fulvestrant, Ribociclib+letrozole, and Abemaciclib+aromatase inhibitors have been tested, some giving encouraging results [143].

Conclusions

At least 12 canonical signaling pathways are activated in cancer, which are partially or completely inactivated in adults. Among these, a leading place is occupied by the RAS–RAF–MEK–ERK signaling pathway, which uses about 39 proteins to take up biological signals from a plethora of extracellular ligases, transmit them transmembrane through 12 receptors that activate the GRB2 protein, the first cytoplasmic member of the signaling pathway (EGFR/ERBB1/HER1, ERBB2/HER2, PDGFRA, PDGFRB, IGFR, KIT/c-KIT, FLT3, MET, FGFR1, FGFR2, FGFR3 and FGFR4), and eight other receptors, BDKRB1, BDKRB2, EDNRA, EDNRB, NTRK1, TPM3, TPR and TFG, of which the first four activate GNAQ and GNA11 proteins and the other four activate RAS proteins directly. This is followed by 11 cytoplasmic and 16 nuclear proteins, through which the RAS–RAF–MEK–ERK signaling pathway stimulates transcription of factors that promote cell proliferation, evasion of apoptosis and angiogenesis. Apart from GRB2, all other members of the RAS–RAF–MEK–ERK signaling pathway undergo mutations in several cancers that render them inactive and reactivate them, which play important roles in tumour development and their incapacitation is a major challenge for oncologists. To date, products have been developed to block the activity of most members of the RAS–RAF–MEK–ERK signaling pathway, some with encouraging results, by reducing the rate of tumour progression, inhibiting or slowing cell proliferation, halting the angiogenic process or driving transformed cells into the programmed cell death pathway. Some products, including Trametinib, Paclitaxel, Binimetinib, Sorafenib, Sunitinib, Afatinib and Gefitinib, act on multiple protein targets, while others, including JNK-IN-8 and Regorafenib, have target specificity, acting selectively on a single protein. The latter category also includes monoclonal antibody-based products, including Trastuzumab, Pertuzumab, Panitumumab, Margetuximab, Xentuzumab, Ganitumab, Onartuzumab, Telisotuzumab, Sintilimab, Cetuximab, Spartalizumab, which biologically disrupt the signaling pathway of targeted proteins. As some tumour cells have developed alternative mechanisms to circumvent the action of the chemotherapeutic agent, through new mutations or separate pathways to sustain progression, oncology research has sought to introduce innovative 2nd or 3rd generation products into treatment regimens, so that the fight for life for researchers and cancer patients is ongoing and always introducing new challenges.

Conflict of interest

The author has no conflict of interest to declare.

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