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1. Introduction

Glioblastoma multiforme (GBM) is the most common primary brain tumor among adults. Rapid tumor progression and diffuse invasion of brain tissue restrict the therapeutic options and result in poor prognosis despite advances in the understanding of this tumor’s molecular biology and pathophysiology [1-4]. Current standard therapy consists of a combination of tumor resection, irradiation and temozolomide. Advances in the field of molecular biology have led to the development of targeted therapy, and the epidermal growth factor receptor (EGFR) has been introduced as one potential therapeutic target [5]. Although pre-clinical studies have shown promising effects, clinical applications yielded no significant benefit in comparison with standard therapy. This fact encouraged extensive investigations studying the molecular mechanisms underlying GBM resistance to EGFR-targeted therapy. Epithelial to mesenchymal transition (EMT) is considered an important factor contributing to resistance towards this therapy by diminishing the molecular target [1-6].

Epithelial to mesenchymal transition is a common process, taking part in organ development, wound healing, tissue remodelling, cancer progression and metastasis. The main features accompanying this mechanism are the loss of epithelial characteristics of cells and the acquisition of mesenchymal markers such as fibronectin, vimentin and N-cadherin. As a result, tumor cells develop increasing invasive and migratory potential. The loss of epithelial features mounts the resistance of tumor cells against targeted therapy directed towards the EGFR. Mesenchymal transition leads to disorganisation of the cytoskeleton, disruption of intercellular adhesions and changes in expression of transcriptional factors, resulting in the development of a more malignant cellular phenotype [1, 2, 7].
In embryogenesis, epithelial to mesenchymal transition appears during gastrulation and activates the formation of the mesodermal layer as the third germ layer after ectoderm and endoderm are built. In addition, EMT is involved in the development of neural crest cells, arising from the dorsal part of the neural tube [7]. This requires a highly specialised program that is necessary to allow the normal development of cells. On the other hand, under pathological conditions, EMT increases the invasiveness and migratory potential of tumor cells, supports their malignant transformation and may lead to resistance of tumor cells towards various therapeutic agents, especially in malignant gliomas.

2. EGFR

The EGFR is a transmembrane glycoprotein belonging to the human EGFR (HER) family, which includes four members (HER 1-4) that share a similar structure. The EGFR/HER1 consists of external and internal domains. The extracellular part possesses a binding sequence for ligands such as EGF, hepatocyte growth factor (HGF), fibroblast growth factor (FGF), insulin-like growth factor-1 (IGF-1) or tumor growth factor-α (TGF-α). The internal domain contains a tyrosine kinase (TK), capable of phosphorylation and activation of a variety of downstream pathways such as phospholipase Cγ, phosphatidylinositol-3-kinase (PI3-K), Janus-activated kinase 2 (JAK-2) and mitogen-activated kinase (MAPK). Human epidermal growth factor family receptors are expressed on many cell types and mediate signal transduction to intracellular compartments and hereby regulate various functions of cells such as proliferation or differentiation [1, 5, 8, 9].

Phosphorylation and dephosphorylation are crucial pathophysiological events within intracellular interactions. A dysregulation of their balance contributes to the development of an invasive cellular phenotype. Upon activation, receptor tyrosine kinases dimerise and autophosphorylate on tyrosine residues, which in turn create complexes with proteins possessing SH2 domains such as GRB2, SHC or signalling proteins PI3-K and SRC [9]. Pathological activation of RAS occurs in numerous cancers. This signalling pathway integrates various diverse stimuli promoting cell transformation, gene expression and tumor progression. RAS is a small guanine triphosphate-binding protein that activates the serine-threonine kinase RAF. RAF phosphorylates the dual specificity kinase MEK, which in turn activates MAPK (ERK). The latter translocate into the nucleus and activate various transcription factors such as the ETS family factors FOS, JUN orSlug (SNAI-2). Thereby RAS propagates the activation of EMT. Moreover, RAS is able to promote EMT by downstream activation of PI3-K or RHO/RAC. PI3-K is involved in cell cycle regulation via phosphorylation of cyclin-dependent kinase inhibitors. In addition, it controls the phosphorylation of proapoptotic proteins and survival of the cell. PI3-K can be activated either via RAS or directly via TK receptors. PI3-K is a lipid kinase, and its activation generates phosphatidylinositol-3,4,5-triphosphate (PIP3) at the inner side of plasma membrane, which furthermore mediates the signalling via the serine-threonine kinase AKT that is able to translocate into the nucleus and take part in gene regulation through phosphatidylinositol-dependent protein kinase-1 (PDK-1) [8, 9, 10].
Epidermal growth factor overexpression and/or mutational activation is the most common molecular alteration in primary GBM and can be detected in far more than 50% of glioblastoma cells [5]. There are several mechanisms that may cause dysfunction of the receptor. Epidermal growth factor receptor gene amplification is the most common reason leading to protein overexpression. Other mechanisms include constitutive receptor activation by deletion-mutation (EGFRvIII) or autocrine overproduction of EGFR ligands [5, 6, 9]. The presence of EGFRvIII is associated with EGFR gene amplification.

3. Therapeutic EGFR inhibitors

Several drugs that target EGFR have been introduced. The TK inhibitors erlotinib and gefitinib compete with adenosine triphosphate to bind to the intracellular TK domain and dissolve further signalling involving PI3-K/AKT and MAPK pathways. Erlotinib was approved in the treatment of metastatic non-small cell lung carcinoma (NSCLC) and in combination with gemcitabine for metastasized pancreatic cancer or pancreatic cancer without the possibility of gross total resection [11, 12]. Gefitinib is used for metastatic NSCLC. Another small molecule EGFR-TK inhibitor represents lapatinib, which affords dual inhibition of EGFR and HER-2 and has been approved for the treatment of advanced or metastatic breast cancer. Unfortunately, the clinical application in gliomas had shown no benefit in comparison to standard therapy [1, 5, 6, 8].

Another possibility to inhibit EGFR signalling consists in the prevention of ligand binding. Monoclonal antibodies such as cetuximab have been introduced and investigated for this purpose. However, their molecular weight impairs their penetration of the blood brain barrier. Often the concentration of the agent is insufficient to yield a significant therapeutic effect within the targeted tissue [13].

Antisense RNA has been introduced as an option to inhibit the EGFR pathway as well. Sense RNA hybridizes to antisense RNA which leads to inhibition of translation. Another strategy to switch off the EGFR cascade is the application of small interfering RNAs. These suppress the homolog genes and result in sequence-specific degradation of mRNA. Furthermore, ribozymes are small RNA molecules that are able to bind and cleave complementary RNA substrates. EGFRvIII-targeted ribozymes have been reported to reverse malignant phenotype of transformed fibroblasts and glioblastoma cells [14, 15]. However, the potential clinical value of these methods remains unknown [16].

4. Molecular principles of EMT

Tumor progression represents an integrated multistep complex of molecular changes that ultimately result in local invasion and dissemination of malignant cells. The cells invade the epithelial basement membrane, infiltrate the surrounding tissue, access the blood circulation and may create new tumor seeds. This dynamic and aggressive process demands
cell-to-cell and cell-to-matrix interactions, degradation and remodelling of extracellular matrix, cytoskeleton reorganisation and gain of migratory behaviour of tumor cells. Epithelial to mesenchymal transition is a differentiation switch which promotes the loss of the epithelial phenotype and facilitates cell motility and invasiveness. One of the crucial steps promoting EMT is the repression of the epithelial marker E-cadherin, a transmembraneous calcium-dependent glycoprotein responsible for cell-cell adhesion, which plays a key role in embryonic development and homeostasis. The intracellular domain of E-cadherin associates with a protein complex involving α-catenin, β-catenin and p120-catenin. Actin proteins bind α-catenin and hereby allow the connection between E-cadherin and the actin microfilament network of the cytoskeleton that forms the shape of the cell. Epithelial cells are typically characterized by apicobasal difference. Thus, the apical compartment faces the lumen, whereas the basolateral surface is located on a basement membrane. Epithelial cells are anchored by specialized cell-to-cell connections, i.e. tight junctions, adherens junction and desmosomes. E-cadherin acts as a tumor suppressor by linking the epithelial cells and keeping them in a stationary rigid state [1, 2, 7, 8, 9, 17].

During EMT, tumor cells loose junctional contact and epithelial cell polarity and acquire typical properties of mesenchymal cells. E-cadherin is a central regulator of the epithelial phenotype, and its downregulation results in the destabilisation of the epithelial architecture. Dysregulation of E-cadherin may be located at various levels, and hypermethylation of the E-cadherin promoter is among the molecular mechanisms [1, 2, 8-10, 17].

Under normal physiological conditions, epithelial cells are separated from the extracellular matrix (ECM) by basement membranes. This barrier prevents the interaction between epithelial cells and their microenvironment. The destabilisation of the basement membrane enables contact between various signalling proteins of the ECM and epithelial cells. The resulting cellular signalling may enhance the progression of EMT by activating different intracellular signalling pathways [17]. Gene transcription regulated by transcription factors is an important mechanism involved in gene regulation. Some transcriptional repressors such as SNAI-1/2, zinc finger E-box binding homeobox-1 (ZEB-1) and ZEB-2 are able to bind directly to the E-cadherin promoter and repress its transcription. Overexpression of these proteins supports mesenchymal transformation and the change of behavioural characteristics and promotes the continuous acquisition of malignant features by tumor cells [18, 19]. Crucial transcription factors involved in EMT are TWIST-1 and signal transducers and activators of transcription-3/-5 (STAT-3/-5). TWIST-1 is a basic helix-loop-helix protein that forms heterodimers binding on DNA, hereby regulating the development and differentiation of cells. For instance, TWIST-1 inhibits p53-mediated apoptosis in rodent fibroblasts or stops normal skeletal muscle development by creating heterodimers with myogenic basic helix-loop-helix proteins (MyoD and myogen). Its function within EMT is repression of the epithelial marker E-cadherin, activation of N-cadherin and hereby promotion of mesenchymal transformation, resulting in a more aggressive phenotype and progression of glioblastoma. TWIST-1 is reported to be an important EMT regulator in other malignancies as well, such as breast, gastric, hepatocellular and prostate cancer. There is significant evidence that TWIST-1 is involved in regulation of programmed cell death and induction of apoptosis. Through inhibition of p53-mediated
apoptosis, TWIST-1 enables cell survival by preventing growth arrest and promotes invasiveness of tumor cells [3, 4]. Moreover, this process may result in increased resistance to various chemotherapeutic agents.

Sex determining region Y-box-2, also known as SOX-2, is another transcription factor that is co-expressed with TWIST-1, playing an important role during the development of the nervous system and tumor progression. Knockdown of SOX-2 results in reduced expression of TWIST-1 [4], promoting EMT and potentially being essential for tumor progression and the development of tumor resistance to EGFR-targeted therapies.

Signal transducer and activator of transcription-3 activation is associated with more malignant tumors and poor prognosis. Its overexpression has been detected in malignant gliomas, and its activation correlates with glioma grade. The STAT protein family is phosphorylated by receptor-associated kinases and builds homo- or heterodimers that translocate to the cell nucleus and play a crucial role in cell cycle progression, EMT, anti-apoptosis and metastasis. Signal transducer and activator of transcription-3 is hereby considered an important factor mediating and converging many cellular pathways. Therefore, either direct or indirect inhibition of STAT-3 may represent an optional therapeutic target in gliomas. Moreover, STAT-3 interacts with EGFR and mediates TWIST-1 expression and TWIST-1-mediated EMT. In addition, there seems to be a correlation between EGFR/EGFR-vIII expression, activation of STAT-3 and glioma grade. Noteworthy, a nuclear interaction between EGFRvIII and STAT-3 leads to malignant transformation of glioma cells [20].

Another interesting point is a recent discovery, described by Lo. He found increased expression of the pro-inflammatory gene cyclooxygenase-2 (COX-2) activated by EGFR-EGFRvIII and STAT-3 cooperation [21]. These interactions represent potential factors contributing to increased resistance of GBM to EGFR-targeted therapy. The important inflammatory enzyme COX-2 is overexpressed in various malignancies. In NSCLC, it has been reported that increased levels of COX-2 contribute to apoptosis resistance, angiogenesis and invasiveness of tumor cells. The effector of COX-2 is prostaglandin E-2 (PGE-2) which is produced by tumorous stromal cells and reduces the expression of E-cadherin via ZEB-1 and SNAI-1. Prostaglandin E-2 activates four G-protein coupled receptors, also known as E-prostanoid receptors-1 to -4 (EP-1 to EP-4), and promotes signalling via the MAPK/ERK cascade, which finally upregulates SNAI-1 and ZEB-1 expression [1, 21, 23]. This loop enhances signalling in the same pathway that is activated by EGFR. In addition, low levels of E-cadherin have been reported to be associated with increased resistance to EGFR-TK inhibitors in NSCLC [21, 23].

Signal transducer and activator of transcription-5 represents an important transcription factor which is involved in the regulation of many genes, facilitating cellular growth, migration and motility. Dimers of STAT-5 bind to specific DNA promoter regions and mediate cellular gene responses. Dysregulation of STAT-5 has been recently described in many malignancies such as prostate, breast and squamous cell cancer of the head and neck (SCCHN). In SCCHN, the activity of STAT-5 results in increased resistance of tumor cells to erlotinib. Moreover, it confers decreased apoptosis following treatment with cisplatin, finally diminishing the clinical effect [19].
The SNAI family members (SNAI-1-3) are related transcriptional repressors. Their SNAG domain at the N-terminal region is responsible for their activity, and their zinc-finger C-terminal region enables the attachment to specific DNA sequences. The main role of SNAI genes is the regulation and promotion of E-cadherin expression. It has been reported that knockdown of SNAI-1 results in decreased invasion and migration of glioma cells. Moreover, SNAI-1 induces expression of matrix metalloprotease-2 (MMP-2), another contributor to EMT progression [18].

Zinc finger E-box binding homeobox-1 regulates transcription of E-cadherin by binding of two zinc finger domains to two E-boxes located in the E-cadherin promoter region. It has been shown that low levels of ZEB-1 improve the sensitivity of cells to erlotinib in head and neck squamous cell carcinoma cell lines [21].

Activator protein-1 (AP-1) is a protein complex consisting of JUN and FOS heterodimers or JUN homodimers. It plays an important role in the regulation of a variety of genes, resulting in the progression of EMT. Induction of AP-1 correlates with MAPK-activation and phosphorylation of the ETS family transcription factors such as E twenty-six-like transcription factor (ELK-1) which furthermore induces the transcription of FOS. Phosphorylated ETS factors result ultimately into the repression of E-cadherin and up-regulation of genes that lead to the transcription of MMPs [2].

As a result of downregulation of E-cadherin, loss of cell-to-cell adhesions and reorganisation of the actin cytoskeleton during EMT, cells acquire a mesenchymal identity. The expression of mesenchymal cytoskeleton proteins such as vimentin and the deposition of ECM proteins such as collagen or fibronectin become dominant and stimulate the activation of integrins and their signalling pathways that promote the migratory potential of cells. Moreover, it has been reported that the level of E-cadherin depends on the phosphorylation state of β-catenin. Tyrosine phosphorylation of β-catenin prevents the binding to E-cadherin and favours the loss of intercellular contact [1, 2, 17].

Endocytosis and proteolytic cleavage of the extracellular domain of E-cadherin are other factors contributing to destabilisation of intercellular adhesion complexes, cell dissociation and EMT. In addition, integrins together with TK receptor activity contribute to the acquisition of an invasive phenotype via SRC. SRC is a non-receptor, SH2-containing cytoplasmic TK which participates in the control of adhesion and migration. SRC signalling contributes to the alteration of the balance between the adhesive and migratory states of cells. SRC stimulates focal adhesion kinase (FAK) that in turn mediates MAPK signalling, leading to the phosphorylation of light chain kinase which ultimately creates phosphomyosin, resulting in increased cell motility and the disorganisation of cell-to-cell adhesions. In addition, SRC is involved in the regulation of numerous proteins of the ECM such as vinculin or paxillin [2, 17].

5. Cancer stem cells

Cancer stem cells have been introduced as cell colonies able to self-renew, proliferate and produce heterogeneous lineages of cancer cells. Hereby they are playing a crucial role in tumor initiation, growth, invasion and recurrence. Epithelial to mesenchymal transition promotes the development of cancer stem-like cells that exhibit mesenchymal phenotypes and acquire multipotent features. Recent studies have provided the evidence of glioma stem cells or brain tumor stem cells [22]. These exhibit a similar phenotype as neural stem cells and in the majority of cases are characterized by surface proteins such as CD133 or nestin [23, 24]. This type of cells exhibits radio-resistance and an abnormal growth pattern. Tumor recurrence is the primary consequence of treatment failure and cause of death in patients suffering from malignant gliomas. Glioma stem cells possess the potential to stimulate the survival of transformed cells and thereby may become a useful therapeutic target [23, 24]. However, a profound understanding of the biological features of these cells will require many more studies.
6. Extracellular matrix and EMT

Tumor cells express matrix metalloproteases (MMPs) which are able to dissolve the ECM and thereby promote tumor invasion, migration and metastasis. Matrix metalloproteases are a group of zinc-dependent endoproteases. Matrix metalloprotease-2 (MMP-2) and MMP-9 are regulated by SNAI-1 and SNAI-2 (SLUG). Epithelial to mesenchymal transition-mediated dysregulation of SNAI-1 and SLUG in turn promotes the activity of MMP-2 and MMP-9 and thereby increases the invasive and migratory activity of tumor cells. Thus, cancer cells undergoing EMT enhance the initiation of metastasis, often involving transforming growth factor-β (TGF-β) and SMAD, and represent a phenotypic subpopulation of cancer cells which promote the dissemination of the malignant disease. Stromelysin, known as MMP-3, promotes EMT through the induction of reactive oxygen species (ROS) that, in turn, results in overexpression of SNAI [2, 8-10, 17].

7. TGF–β

Transforming growth factor-β has been reported as a strong inducer of EMT. This protein belongs to the TGF-β superfamily and exhibits three isoforms, i.e. TGF-β1, TGF-β2 and TGF-β3, all of which are involved in cell proliferation and differentiation. Transforming growth factor-β is able to induce apoptosis in numerous cell types via the Smad pathway. In addition, TGF-β may recruit non-Smad signalling, for instance the MMP cascade, to promote the malignant transformation of cells. The TGF-β response results in Smad 2 and Smad 3 activation through C-terminal phosphorylation [7, 8].

Transforming growth factor-β signalling finally regulates the expression of SNAI, ZEB and TWIST proteins that, in turn, influence the expression of proteins such as claudin, desmoplakin, MMPs or fibronectin. In this context, TGF-β functions as an important regulator of EMT [7, 8].

Promoted by TGF-β, SNAI-1 and SNAI-2 (SLUG) levels are increased during EMT. Hepatocyte growth factor, FGF and EGF induce the RAS-MAPK or PI3K-AKT pathways that lead to the activation of SNAI expression. The increased expression of SNAI-1 or SNAI-2 enhances the expression of vimentin and fibronectin, reduces E-cadherin and plakoglobin levels and hereby switches on mesenchymal transformation. During embryological development, this process takes care of mesodermal layer and neural crest development. In addition, SNAI proteins inactivate a variety of epithelial proteins such as occludin and claudin. SNAI-1 represses the expression of claudin 3, claudin 4 and claudin 7 and regulates the expression of desmosome proteins such as desmoplakin. SNAI-1 and SNAI-2 decrease the expression level of claudin 1 and occludin. Furthermore, increased SNAI protein activity stimulates the expression of mesenchymal proteins such as Rho-like GTPases which are composed of RHO, RAC and CDC-42 proteins that influence cytoskeleton architecture and cell motility. RHO and RAC regulate E-cadherin activity and adhesiveness of cells, and their activity is among the important determinants of EMT. TGF-β activates the signalling cascade downstream of RHO. The
main RHO effector in TGF-β response is ROCK activity which regulates different processes involved in cell migration such as cytoskeleton reorganisation [1, 2, 7, 8, 17, 18].

Transforming growth factor-β activates TK receptors via PI3-K that, in turn, controls AKT in diverse cells. AKT is an important regulator of various signalling cascades, controlling cell survival, migration and proliferation. Activation of the PI3K-AKT cascade plays a crucial role in EMT.

The WNT protein plays a significant role in the process of mesenchymal transformation as well. WNT is connected downstream to β-catenin, builds adherens junctions and connects E-cadherin to the cytoskeleton through α-catenin. The WNT glycoprotein binds to the transmembrane Frizzled receptor that activates Dishevelled, which in turn prevents phosphorylation of β-catenin by inhibition of glycogen synthase kinase-3β (GSK-3β) and hereby stops its ubiquitination and degradation. This step increases the level of cytoplasmic β-catenin that ultimately translocates into the nucleus and builds complexes with T-Cell factor (TCF) and lymphoid enhancer factor-1 (LEF-1). These related transcription factors mediate the gene response by activating genes required for EMT such as SLUG, ETS and JUN or fibronectin and vimentin. In addition, the basic feature of EMT, downregulation of E-cadherin, increases the level of cytosolic free β-catenin itself. Similarly, the activation of PI3K-AKT and integrin-linked kinase (ILK) inhibits GSK-3β and hereby contributes to EMT progression. Moreover, the activity of NF-κB correlates with the expression of ZEB-1, ZEB-2 and TWIST, which are other strong inducers of EMT [28].

8. Nuclear factor–κB

Nuclear factor-κB (NF-κB) belongs to a family of transcriptional factors, whose activity is important for the maintenance and promotion of the invasive phenotype in cancer cells. Nuclear factor-κB binds DNA sequences as hetero- or homodimers and consequently regulates various cellular processes. Several genes encoding proteins that are involved in the cell cycle (Cyclin D1, c-MYC), cell adhesion (vascular cell adhesion protein) or inflammation (interleukin-2, interleukin-6, interleukin-8) are regulated in this way. Even if NF-κB is ubiquitous, its activity is detected mostly in mature B-lymphocytes [28, 29].

The inhibitor protein IκB plays a crucial role in the degradation of NF-κB and has been discovered in breast cancer. Signalling via NF-κB results in increased expression of SNAI-1 and hereby contributes to EMT progression. Moreover, the activity of NF-κB correlates with the expression of ZEB-1, ZEB-2 and TWIST, which are other strong inducers of EMT [28].

Vimentin, a 56-kDa intermediate filament protein, contributes to mesenchymal transformation of the cell. Cells acquire a spindle-shape form and loosen their connections to neighbouring cells. Studies of vimentin-knockdown mice have shown significantly re-
duced wound healing abilities. In addition, vimentin expression promotes the migration of cancer cells. Nuclear factor-κB activates the vimentin promoter and thus increases the expression of vimentin [28].

9. Resistance to EGFR–targeted therapy

Epithelial to mesenchymal transition is considered an important factor contributing to the resistance of glioma cells against EGFR-targeted therapy. On the other hand, alternative potential explanations of this phenomenon have been suggested.

Glioblastomas exhibit a high degree of intrinsic heterogeneity with a variety of signalling pathways that mediate the subcellular actions. In the case of EGFR inhibition, alternative downstream pathways may be activated and potentiated. A functional-switch could lead to the survival of the cells and, by clonal selection, to the acquisition of resistance to specific therapeutic agents that inhibit one specific signalling pathway.

Phosphatase and tensin homolog is a tumor suppressor protein which dephosphorylates phosphatidylinositol (3, 4, 5)-triphosphate and hereby negatively regulates the AKT signalling axis. Phosphatase and tensin homolog is often mutated in GBM cells which promotes the activity of mTOR resulting in tumor progression. The inhibition of this dominant pathway may lead to alteration of the hierarchy in TKs such as platelet-derived growth factor receptor (PDGFR), JAK2 or cellular mesenchymal-epithelial transition factor (c-MET) [9, 29]. Platelet-derived growth factor receptor is the second most common TK receptor amplified in GBMs. Moreover, MET is also amplified in some GBMs. Concomitant presence of gene amplifications within GBMs may activate and potentiate alternative signalling pathways during inhibitory targeting of EGFR and hereby contribute to increased resistance of glioma cells to erlotinib or other TK-inhibitors [29].

10. Conclusion

The EGFR has been introduced as a therapeutic target in some malignancies. Unfortunately, in GBM, there has been no demonstrable benefit of this approach in comparison to standard therapy. Epithelial to mesenchymal transition is considered an important factor contributing to failure of this therapy by diminishing the molecular target. This phenomenon leads to the loss of epithelial characteristics of cells and to the expression of mesenchymal features. The acquisition of increased motility and invasiveness by glioma cells represents an essential prerequisite for subsequent tumor recurrence and malignant progression. Epithelial to mesenchymal transition is primarily regulated through signalling pathways affecting E-cadherin, a transmembraneous protein responsible for intercellular cell contact. Molecular changes are promoted by a variety of external stimuli. The identification and better understanding of these processes may enable the development of new therapeutic strategies.
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