Tumor trees as a therapeutic target

Targeted treatment directed predominantly against the tumor cells themselves can be divided into three groups - they are drugs that inhibit the self-renewal of tumor cells, drugs that inhibit proliferation and inducers of apoptosis.

Inhibition of proliferation

1. Inhibition of receptor tyrosine kinases

Receptors with intrinsic tyrosine kinase activity (RTK) are among the key structures in cell signaling. Gene, which encode them are among the longest known and their mutations plays a crucial role in the pathogenesis of a wide range of malignancies. Under normal conditions, the receptor weighs growth factors – mitogen– produced by different cells of the microenvironment. Mitogenic signals are transferred to the nucleus through a series of signaling cascades, where they are activated transcription factors necessary to trigger mitosis. In healthy cells, this signaling is physiological and the transmission of a given signal occurs only in the presence of a certain transcription factor (ligand-dependent signaling). However, if RTK genes are deregulated in a tumor cell, ligand-independent signaling may propagate aberrant proliferative signal. This fact is the basis of malignant transformation and proliferation of tumor cells.

In order to eliminate aberrantly activated RTKs, two different therapeutic strategies have been developed - monoclonal antibiotics targeting the extracellular receptor portion of RTK and low molecular weight tyrosine kinase inhibitors (TKIs) blocking the intracellular tyrosine kinase domain of RTK.

EGFR / ERBB / HER Family

(epidermal growth factor / erythroblastosis receptor B / human epidermal growth factor receptor)

Of the antibodies targeting the extracellular receptor domain in the name of these receptors, **cetuximab** and **panitumumab** are used in clinical practice to treat colorectal cancer and **trastuzumab** to treat breast cancer. A new alternative is the so-called chimeric immunoreceptors, where a monoclonal antibody with affinity for a given mitogen binds to tumor cells with its Fc fragment and acts as a competitive inhibitor of real receptors. Of the low molecular weight inhibitors, only **erlotinib** is approved for clinical use.

IGFR Family

(Insulin-like growth factor receptor)

Pathological activation of IGF1R is involved in aberrant mitogenic stimulation in many malignancies. A number of monoclonal antibodies are in clinical trials.

PDGFRA a PDGFRB

(platelet-derived growth factor α/β)

TKIs with activity against PDGFR include, for example, imatinib.

FLT3

(FMS-like tyrosine kinase 3)

This signaling pathway is important for the normal proliferation of hematopoietic progenitors. Receptor tyrosine kinase FLT3 is the most frequently mutated protein in patients with AML. Specific low molecular weight FLT3 inhibitors include, for example, **lestaurtinib**.

MET/HGFR

This receptor binds the only known ligand, hepatocyte growth factor (HGF). Its mutation have been described in stomach cancer. Overexpression has been described in various types of tumors, and signaling through this receptor plays an essential role in the angiogenesis and metastasis of tumor cells. Several blocking monoclonal antibodies are in clinical trials.

KIT/CD117

It binds the so-called KIT ligand (otherwise also stem cell growth factor or mast cell growth factor-SCF). KIT plays an important role in hematopoiesis and melanogenesis. Cytogenetic aberrations of KIT are found in patients with AML , systemic mastocytosis, and mesenchymal tumors of the gastrointestinal tract. TKIs with KIT activity include, for example, **imatinib**.

FGFR

(Fibroblast growth factor receptor)

Activation of these receptors affects proliferation, apoptosis, motility and angiogenesis - thus occurring in a variety of malignancies. Deregulation of FGFR signaling has been associated with a more aggressive tumor phenotype , including increased angiogenesis and early metastasis.

2. Inhibition of non-receptor proteins with tyrosine kinase activity

Non-receptor tyosine kinase proteins play an important role in converting signals from cellular receptors to downstream effector molecules. Protein tyrosine kinases (PTKs) integrate a number of signals from the external environment and thus represent other key regulators of cell proliferation and motility. PTK, together with RTK, is one of the classical oncogenes whose aberrant activation plays a dominant role in malignant transformation. Drugs from the group of tyrosine kinase inhibitors are also similarly used in targeted therapy.

SRC

(cellular Rous sarcoma viral oncogene homolog)

This non-receptor kinase is the **first ever** historically defined oncogene. SRC binds with its SH2 domain to phosphorylated tyrosine residues of the intracytoplasmic part of dimer activated RTKs and is significantly involved in the transmission of mitogenic environmental signals from RTK to intracellular signaling pathways including MAPK or FAK (focal adhesion kinase). SRC is also a major mediator of signal transduction from most integrin receptors, thereby fundamentally regulating cell adhesion, motility, and neovascularization. Therefore, dysregulation of SRCs in tumors is associated with greater invasiveness and metastasis. Due to the fact that dysregulation of SRC in tumors has been described in many solid tumors and hematological malignancies, SRC represents an important target of anticancer therapy. SRC inhibitors include the dual inhibitors **dasatinib** and **bosutinib** , which specifically bind not only SRC but also c-ABL.

FAK

(focal adhesion kinase)

FAK, together with SRC, plays an irreplaceable role in the transduction of signals from integrin receptors. Several low molecular weight FAK inhibitors have been developed for anticancer therapy. Although pharmacological inhibition of FAK reduced the motility and invasiveness of tumor lines in preclinical models, it was shown that the investigated lines often had a compensatory increase in the expression of another PTK, called FAK / PYK2. Therefore, a dual FAK / PYK2 inhibitor was proposed, which showed a significant antitumor effect in the model, including inhibition of neovascularization. The results of clinical trials are expected.

ABL/cABL

(Abelson tyrosine kinase)

This non-receptor PTK is structurally similar to SRC kinase. Fusion of c-ABL and BCR genes underlies chromosomal translocation of BCR-ABL in patients with CML, the most common recurrent c-ABL mutation in human malignancies.

3. Inhibition of RAS protein

Various somatic mutations can cause constitutive activation of RAS proteins, resulting in ligand-independent signaling and subsequent uncontrolled proliferation of tumor cells. RAS, along with p53 , is one of the two most frequently mutated proteins in solid tumors. Farnesyltransferase (FTI) and, more recently, geranylgeranyltransferase (GGTI) inhibitors appear to be promising substances in preclinical studies. These substances catalyze a key post-translational modification of the RAS protein, namely prenylation (attachment of an isoprenyl lipid chain). Prenylation allows the RAS to be anchored to the inner side of the cell membrane and facilitates interactions with effector proteins. FTI / GGTI thus indirectly interfere with the function of RAS - they inactivate it. Drugs that have already undergone clinical trials include **tipifarnib** or **lonafarnib** . Other substances that inhibit prenylation include, for example, **bisphosphonates** .

4. Inhibition of the RAF-MEK-ERK signaling pathway

More than a dozen downstream effector molecules of the RAS protein are currently known. Mitogen-activated protein kinase (MAPK) cascades are among the best-studied signaling pathways triggered by RAS activation, in particular the RAF-MEK-ERK cascade (RAS-associated factor-mitogen-activated protein kinase ERK kinase 1-extracellular signal-related kinase). **Sorafenib** is an inhibitor with activity against RAF. It is used to treat advanced forms of kidney cancer and liver cancer.

5. Inhibition of the JAK-STAT cascade

Janus kinase-signal transducers and activators of transcription (JAK-STAT) are the second largest group of receptors for a number of cytokines. Most interleukins, hematopoietic growth factors (EPO, TPO, GM-CSF) and all interferons bind to this type of receptor. JAK proteins are **non-receptor PTKs** whose activation takes place downstream from cytokine-aggregated receptors. Activated JAK proteins phosphorylate specific intracytoplasmic sites of cytokine receptors, leading to the attraction of STAT cytoplasmic proteins, which are phosphorylated by JAK active kinases upon anchoring to the receptor. Phosphorylated STAT proteins form homo- and heterodimers and

translocate to the nucleus, where they anneal to specific promoters in DNA and regulate transcription of target genes. In addition, STAT proteins can be activated by other non-receptor PTKs, such as SRC or ABL. There are several inhibitors of the JAK-STAT signaling pathway in preclinical and clinical testing. IL-6 receptor superantagonist, **Sant7 monoclonal antibody**, shows an antitumor effect in preclinical models by blocking the JAK-STAT signaling pathway. Another strategy is to inhibit PTKs downstream of the receptors. **Tryphostin** and **lestaurtinib** are JAK2 inhibitors, dosatinib and bosutinib inhibit SRC. Both approaches lead to efficient suppression of STAT transcription factors.

6.Protein kinase C inhibition

Protein kinase C includes a group of **serine / threonine kinases**. Phospholipase C (PLC) plays a key role in PKC activation, cleaving PIP-2 into IP3 and DAG on the inside of the membrane. While DAG remains part of the membrane, cleaved IP3 diffuses through the cytoplasm and activates the calcium channels of the endoplasmic reticulum, leading to an increase in intracellular calcium concentration. Classical PKCs then need both calcium ions and DAGs for activation. PKC deregulation plays an important role in oncogenesis. Increased PKC expression leads to activation of RAS-RAF-MEK-ERK, which stimulates increased transcription of anti-apoptotic molecules, accelerated cell growth and proliferation. Natural PKC inhibitors are, for example, the bacterial product staurosporine or the marine mollusc product bryostatin. In addition to natural inhibitors, low molecular weight PKC inhibitors have been synthesized, but they have significant side effects because they inactivate other substrates. This includes e.g.**midostaurin** or **enzastaurin** .

7. Proteasome inhibition

Proteasomis a multiprotein catalytic complex responsible for the controlled degradation of intracellular proteins. Proteins to be degraded are labeled with a polyubiquitin chain and subsequently degraded to oligopeptides in the proteasome. This mode of degradation of intracellular proteins is referred to as the ubiquitin-proteasome system. Protein degradation in the proteasome allows all cells to destroy old, damaged, non-functional or pathological proteins and expose their peptides in complex with HLA class I molecules on the cell surface. In addition to this liquidation-presentation task, the ubiquitin-proteasome system is one of the other physiological regulators of the expression of a number of proteins. The proteasome regulates the expression level of important mediators of cell growth, proliferation, apoptosis or angiogenesis. Proteasome substrates include, for example, some anti-apoptotic proteins. Thus, increased proteasome activity may lead to inhibition of apoptosis and accelerated cell cycle transit. Reversible proteasome inhibitors include bortezomib, irreversible proteasome inhibitors include carfilzomib or other so-called new generation proteasome inhibitors.

Inhibition of self-renewal

1. Inhibition of telomerases

Telomeres are terminal structures of chromosomes characterized by a nucleotide repeating sequence (TTAGGG) n. Sufficiently long telomeres form protective structures with a specific three-dimensional conformationat the ends of chromosomes - so-called **closed telomeres**- which prevents the end of the DNA from being recognized as a double break, resulting in aberrant chromosomal fusions. The average length of telomeres is 1000 bases and with each division they shorten by 30-100 kbp. Telomerase is a reverse transcriptase that has the ability to elongate telomeres. Physiologically, telomerase is expressed only in a subpopulation of stem and germ cells, thus keeping their number constant. Cells that have entered the differentiation process and are not expressed in telomerase-differentiated cells. In tumors, more than 90% of cases are **aberrant reexpressed**, whereby the tumor cells acquire the ability of infinite renewal, ie immortality. Telomeres and telomerase represent potential targets in experimental therapy of malignancies. There are a number of therapeutic approaches focused on telomeres or telomerases - low molecular weight inhibitors, antisense oligonucleotides, RNA interference, gene therapy or immunotherapy. It is important to note that highly specialized telomerase inhibitors induce tumor cell death with a considerable delay, as tumor cells must first be critically shortened by telomeres - this will only happen after several cell divisions. Another strategy for aberrantly activated telomerases in tumors is the introduction of gene-directed enzyme prodrug therapy (GDEPT) into tumor cells .

2. Inhibition of signaling cascades involved in the regulation of self-renewal

Deregulation of signaling pathways that play a role in maintaining stem cell homeostasis leads, for example, to their endless self-renewal and differentiation disorders. Targeted inhibition of these pathways could be a new effective tool in antitumor control. These include, for example, inhibition of the NOTCH signaling pathway, which plays an important role in embryogenesis, regulation of stem cells and their subsequent differentiation, and blockade of TGFβ, BMP and SMAD - negative regulators of hematopoietic stem cells.

Induction of apoptosis

1. Direct induction of apoptosis

Death receptor agonists

The binding of so-called lethal ligands to specific receptors leads to the triggering of an external (extrinsic) apoptotic pathway. **Deadly ligands** include natural type II TNF family transmembrane cytokines, such as TNFα, FAS ligand, and TNFSF10 / TRAIL (TNF-related apoptosis-inducing factor). TNFα is one of the longest known

cytokines and has significant proapoptotic activity. However, systemic administration already induced a severe septic shock-like alteration of test animals in preclinical models. Currently, TNFα is used only in topical therapy in patients with soft tissue sarcomas or limb metastases of malignant melanoma. Because the systemic use of FASLG has made it impossible to alter its extreme hepatotoxicity, only **TNFSF10 / TRAIL is currently used of the above-mentioned lethal ligands**., in a number of malignancies. TRAIL selectively kills tumor cells, while normal, healthy cells are resistant to TRAIL.

Induction of ROS and arsenic oxide

Targeted induction of reactive oxygen species formation in tumor cells represents a possible antitumor strategy. Clinically tested inducers include elesclomol. Arsenic oxide is used to treat promyelocytic leukemia. At higher concentrations, it triggers apoptosis by inducing oxidative stress.

2. Indirect induction of apoptosis

Inhibition of antiapoptotic BCL2 proteins

BCL2 family proteins are among the basic **regulators of** programmed cell death. Based on the knowledge of the structure and functional interaction of BCL2 proteins, a number of low molecular weight substances were synthesized, which functionally mimic anti-apoptotic BCL2 proteins from the group of so-called **BH3-mimetics** . These bind to the BH3 binding site of BCL2 antiapoptotic proteins, causing the release of the effector proapoptotic proteins **BAX** and **BAK** from binding to BCL2 antiapoptotic proteins. This leads to a direct apoptotic effect. These include, for example, non -specific **gossypol** or **obatoclax** or specific ABT-737.

Inhibition of heat shock proteins

Heat shock proteins (HSPs) form a group of related proteins whose expression is **induced by** various environmental **stress signals** . HSPs act in the cell as so-called **chaperones** - proteins capable of binding other, so-called client proteins and changing their conformation. Under physiological conditions, chaperones help to assemble newly synthesized proteins and participate in their transport between organelles. In addition, HSPs play an important cytoprotective role in stabilizing stress-damaged proteins. Thus, the increased HSP expression found in many malignancies has a marked antiapoptotic effect. **Of the pharmacological HSP inhibitors, HSP90** inhibitors are in clinical trials .

Induction of p53

p53 is an important proapoptotic mediator of genotoxic stress and oncogenic signaling. Most conventional cytostatics are among the main inducers of genotoxic stress. The major negative physiological regulator of p53 expression is E3 ubiquitin ligase MDM2, which maintains low p53 expression by stimulating ubiquitin proteasomal degradation. Many malignancies (leukemias, sarcomas) show pathological overexpression of MDM2 with subsequent functional suppression of the p53 signaling pathway, which has a comparable effect as p53 gene aberrations. For therapeutic purposes, low molecular weight **inhibitors of MDM2** called **nutlins** (eg Nutlin-3) have been developed.

Links

related articles

- Protein degradation
- Cell degradation system
- Ubiquitination
- Deubiquitination
- History of the ubiquitin-proteasome system
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References

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