Tumor stroma as a therapeutic target

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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 apoptosis inducers*.

Inhibition of proliferation

1. Inhibition of receptor tyrosine kinases

Receptors with intrinsic tyrosine kinase activity (RTKs) are among the key structures in cell signaling. The genes that encode them are among the longest known, and their mutation plays a fundamental role in the pathogenesis of a wide range of malignancies. Under normal conditions, **growth factors** - mitogens - produced by various cells of the microenvironment bind to receptors. Mitogenic signals are transduced via a series of **signaling cascades** into the nucleus, where the transcription factors necessary for the initiation of mitosis are activated. In healthy cells, this signaling is physiological and the given signal is transmitted only in the presence of a certain transcription factor (ligand-dependent signaling). However, if there is a **deregulation of RTK genes** in a tumor cell, the propagation of an aberrant proliferation signal independent of the presence of a growth factor (ligand-independent signaling) can occur. 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 antibodies targeting the extracellular receptor part of RTKs and low molecular weight tyrosine kinase inhibitors (TKIs) blocking the intracellular tyrosine kinase domain of RTKs.

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 the receptors, **cetuximab** and **panitumumab** are used in clinical practice to treat colorectal cancer and **trastuzumab** to treat breast cancer. A new alternative is represented by so-called chimeric immunoreceptors, where a monoclonal antibody with an affinity for a given mitogen binds with its Fc fragment to tumor cells 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 testing.

PDGFRA and PDGFRB

(platelet-derived growth factor α/β)

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

FLT3

(FMS-like tyrosine kinase 3)

This signaling pathway is important for 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, which is hepatocyte growth factor (HGF). Its mutations have been described in carcinoma of the stomach. Overexpression has been described in various types of tumors and signaling through this receptor plays an essential role in angiogenesis and metastasis of tumor cells. Several blocking monoclonal antibodies are in clinical testing.

KIT/CD117

It binds the so-called KIT ligand (otherwise also growth factor for stem cells or growth factor for mast cells-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 activity against KIT include, for example, **imatinib**.

FGFR

(Fibroblast growth factor receptor)

The activation of these receptors affects proliferation, apoptosis, motility and angiogenesis - it therefore occurs in a variety of malignancies. Deregulation of FGFR signaling is 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 **transducing 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. Together with RTK, PTK belongs to the classical oncogenes, whose aberrant activation plays a dominant role in malignant transformation. Drugs from the group of tyrosine kinase inhibitors are similarly used in targeted therapy.

SRC

(cellular Rous sarcoma viral oncogene homolog)

This non-receptor kinase is the **first** historically defined oncogene. SRC binds with its SH2 domain to phosphorylated tyrosine residues of the intracytoplasmic part of the dimer of activated RTKs and is significantly involved in the transmission of mitogenic signals from the external environment from RTKs 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 crucially regulating cell adhesion, motility, and neovascularization. Therefore, dysregulation of SRC in tumors is associated with their greater invasiveness and metastasis. Since SRC dysregulation in tumors has been described in many solid tumors as well as hematologic malignancies, SRC represents an important target for antitumor therapy. SRC inhibitors include the dual inhibitors **dasatinib** and **bosutinib**, which specifically target c-ABL in addition to SRC.

FAK

(focal adhesion kinase)

FAK plays, together with SRC, an irreplaceable role in the transduction of signals from integrin receptors. Several small molecule FAK inhibitors have been developed for antitumor therapy. Although pharmacological inhibition of FAK reduced the motility and invasiveness of tumor lines in preclinical models, it was shown that the examined lines often had a compensatory increase in the expression of another PTK, called FAK/PYK2. Therefore, a dual FAK/PYK2 inhibitor was designed, which demonstrated a significant antitumor effect in the model, including inhibition of neovascularization. Clinical trial results are awaited.

ABL/cABL

(Abelson tyrosine kinase)

This non-receptor PTK is structurally similar to SRC kinase. Fusion of the c-ABL and BCR genes underlies the chromosomal translocation 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 is, together with p53, among the two most frequently mutated proteins in solid tumors. In preclinical studies, farnesyltransferase inhibitors (FTI) and more recently also geranylgeranyltransferase (GGTI) appear to be promising substances. These substances catalyze a key post-translational modification of the RAS protein, namely prenylation (attachment of an isoprenyl lipid chain). Prenylation enables anchoring of RAS to the inner side of the cell membrane and facilitates interactions with effector proteins. FTI/GGTI thus indirectly interfere with the function of the RAS - they inactivate it. Medicines that have already undergone clinical trials include **tipifarnib** and **lonafarnib**. Other substances that inhibit prenylation include, for example, **biphosphonates**.

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

Currently, more than a dozen downstream effector molecules of the RAS protein are known. Among the best-studied signaling pathways triggered by RAS activation are the mitogen-activated protein kinase (MAPK) cascades, especially the RAF-MEK-ERK (RAS-associated factor-mitogen-activated protein kinase ERK kinase 1-extracellular signal-related kinase) cascade. **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 HOW-STAT cascade

Receptors associated with **JAK-STAT** (Janus kinase-signal transducers and activators of transcription) represent the second large group of receptors for a whole range of cytokines. Most interleukins, hematopoietic growth factors (EPO, TPO, GM-CSF) and all interferons bind to this type of receptors. JAK proteins belong to the **non-receptor PTKs** whose activation occurs downstream of cytokine-aggregated receptors. Activated JAK proteins phosphorylate specific intracytoplasmic sites of cytokine receptors, leading to the attraction of cytoplasmic STAT proteins, which are phosphorylated by active JAK kinases after anchoring to the receptor. Phosphorylated STAT proteins form homo- and heterodimers and translocate to the nucleus, where they attach to specific promoters in DNA and regulate the transcription of target genes. In addition, STAT proteins can be activated by other non-receptor PTKs, e.g. SRC or ABL. There are several inhibitors of the JAK-STAT signaling pathway in preclinical and clinical testing. IL-6 receptor superantagonist, the monoclonal antibody **Sant7**, exhibits antitumor activity 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. Inhibition of protein kinase C

Protein kinase C includes the group of **serine/threonine kinases**. A key role in PKC activation is played by phospholipase C (PLC), which cleaves PIP-2 into IP3 and DAG on the inner side of the membrane. While DAG remains part of the membrane, cleaved IP3 diffuses through the cytoplasm and activates endoplasmic reticulum calcium channels, leading to an increase in intracellular calcium concentration. Classic PKCs then need both calcium ions and DAG for activation. Deregulation of PKC plays an important role in oncogenesis. Increased PKC expression leads to RAS-RAF-MEK-ERK activation, which stimulates increased transcription of anti-apoptotic molecules, accelerated cell growth and proliferation. Natural inhibitors of PKC 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, as they also inactivate other substrates. These include, for example, **midostaurin** or **enzastaurin**.

7. Proteasome inhibition

The **Proteasome** is a multiprotein catalytic complex responsible for the controlled degradation of intracellular proteins. Proteins intended for degradation are marked with a polyubiquitin chain and subsequently degraded into oligopeptides in the proteasome. This way of degrading intracellular proteins is referred to as the ubiquitin-proteasome system. Degradation of proteins in the proteasome allows all cells to dispose of old, damaged, non-functional or pathological proteins and expose their peptides in complex with HLA class 1 molecules on the cell surface. In addition to this liquidation-presentation role, the ubiquitin-proteasome system belongs to other physiological regulators of the expression of a whole range 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. Increased proteasome activity can therefore lead to inhibition of apoptosis and accelerated passage through the cell cycle. Reversible proteasome inhibitors include bortezomib, irreversible ones include carfilzomib or other so-called new generation proteasome inhibitors.

Inhibition of self-renewal

1. Telomerase inhibition

Telomeres are terminal structures of chromosomess characterized by a repeating sequence of nucleotides (TTAGGG)n. Sufficiently long telomeres create protective structures with a specific three-dimensional conformation at the ends of chromosomes - the so-called **closed telomeres** - which prevent the end of the DNA from being recognized as a double-stranded break and thus aberrant chromosomal fusions. The average length of telomeres is 1000 bases, and they shorten by 30-100 kbp with each division. Telomerase is a reverse transcriptase that has the ability to lengthen telomeres. Physiologically, telomerase is expressed only in a subpopulation of stem and germ cells, keeping their number constant. Cells that have entered the differentiation process and differentiated cells do not express telomerase. In tumors, in more than 90% of cases, its **aberrant re-expression** occurs, whereby tumor cells acquire the ability of infinite renewal, i.e. immortality. Telomeres and telomerase represent potential targets in the experimental therapy of malignancies. There are a number of therapeutic approaches focused on telomeres or telomerase - low molecular weight inhibitors, antisense oligonucleotides, RNA interference, gene therapy or immunotherapy. It is important to note that highly specific telomerase inhibitors induce tumor cell death with a significant delay, as tumor cells must first undergo critical telomere shortening—this occurs after several cell divisions. Another strategy affecting aberrantly activated telomerase in tumors is the introduction of so-called **suicide genes** (GDEPT, gene-directed enzyme prodrug therapy) 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 the homeostasis of stem cells leads, for example, to their endless self-renewal and differentiation disorders. Targeted inhibition of these pathways could represent a new effective tool in the fight against cancer. This includes, for example, the inhibition of the NOTCH signaling pathway, which plays an important role in embryogenesis, the regulation of stem cells and their subsequent differentiation, or the 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 the external (extrinsic) apoptotic pathway. The **death ligands** include natural type II transmembrane cytokines from the TNF family, e.g. TNFα, FAS ligand and TNFSF10/TRAIL (TNF-related apoptosis-inducing factor). TNFα is among the longest-known cytokines and has significant pro-apoptotic activity. Systemic administration, however, already in preclinical models caused a severe alteration of the tested animals, similar to septic shock. Currently, TNFα is only used in local therapy in patients with soft tissue sarcomas or extremity metastases of malignant melanoma. Due to the fact that the systemic deployment of FASLG has been made impossible for a change by its extreme hepatotoxicity, currently only **TNFSF10/TRAIL** is used among the aforementioned deadly ligands, and that in a whole range of malignancies. TRAIL selectively kills tumor cells, while normal, healthy cells are resistant to TRAIL.

Induction of ROS and arsenic oxide

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

2. Indirect induction of apoptosis

Inhibition of anti-apoptotic 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 have been synthesized that functionally mimic the anti-apoptotic BCL2 proteins from the so-called **BH3-mimetic** group. These bind to the BH3 binding site of BCL2 anti-apoptotic proteins, which causes the release of the effector pro-apoptotic proteins **BAX** and **BAK** from binding to BCL2 anti-apoptotic proteins. This leads to a direct apoptotic effect. These include, for example, the non-specific **gossypol** or **obatoclax** or the specific ABT-737.

Inhibition of heat shock proteins

Heat shock proteins (HSPs) form a group of related proteins whose expression is **induced** by various **stress signals** from the external environment. 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 fold newly synthesized proteins and participate in their transport between organelles. In addition, HSPs have an important cytoprotective role, as they stabilize stress-damaged proteins. The increased expression of HSP found in many malignancies therefore has a significant anti-apoptotic effect. Of the pharmacological HSP inhibitors, the **HSP90 inhibitors** are at the stage of clinical testing.

Induction of p53

p53 is an important proapoptotic mediator of genotoxic stress and oncogenic signaling. Major inducers of genotoxic stress include most conventional cytostatics. The main negative physiological regulator of p53 expression is the E3 ubiquitin ligase MDM2, which by stimulating the ubiquitin proteasomal degradation of p53 keeps its expression at a low level. A whole range of malignancies (leukemia, sarcomas) show pathological overexpression of MDM2 with subsequent functional suppression of the p53 signaling pathway, which has a comparable effect to p53 gene aberrations. Low molecular weight **MDM2 inhibitors** called **nutlins** (e.g. Nutlin-3) have been developed for therapeutic purposes.

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