Signal transduction elements as therapeutic targets in oncology

Basic characteristics of transformed cells and tumour formation and development:

- Ability to proliferate, reduced need for external proproliferative stimulation
- Resistance to apoptosis
- Capacity for invasive growth and metastasis
- Evasion of immune surveillance
- Capacity for neoangiogenesis

Tumor treatment options

Portfolio of concepts in the oncology treatment arsenal:

- Surgical approaches
- Radiotherapy
- Chemotherapy
- Photodynamic therapy
- Immunotherapy
- Gene therapy

Classical chemotherapeutic approaches can be divided into c**hemoprevention, "classical" chemotherapy**, which suppresses cell proliferation in various ways, **epigenetic chemotherapy**, hormonal therapy and induction of differentiation. Many of the drugs used in these areas have been found by empirical approaches. They stop proliferation by acting at the level of transcription, translation, proteosynthesis or cell division itself.

A rational approach to the treatment of cancer requires knowledge of the molecular basis of its pathogenesis and the identification of applicable specific molecular targets within that framework. Transformed cells constitute a minority population in most tumours, closely "collaborating" with cells of the tumour stroma (fibroblasts, vascular structures, immune system cells). Therefore, possible therapeutic targets are sought not only at the level of the transformed cells themselves, but also within the complex tumor microenvironment, at the level of tumor and stromal cells and their mutual communication.

Targeted treatment of tumours

A conceptually new group of chemotherapy is "targeted" or "designer therapy". In contrast to 'conventional' chemotherapy, which, despite a certain degree of preference for transformed cells, also affects other proliferating cell populations in the body (bone marrow cells, epithelial cells, etc.), it targets signal transduction pathway molecules characteristic of pathological proliferation or resistance to apoptosis of tumour cells and the oncogenetic processes induced by them. The ideal target of intervention is the cancer stem cell, which, unlike its more differentiated products, is capable of sustained self-renewal.

From this perspective, molecules of signaling pathways involved in regulation represent possible "sources" of therapeutic targets:

1. **Stem cell self-renewal**

- Telomerase inhibitors
- Gamma-secretase inhibitors (Notch signaling pathway)
- Inhibition of the Wnt-beta-catenin signaling pathway
- Sonic Hedgehog signaling pathway inhibition

2. **Proliferation/progenitor cell cycle**

- Inhibition of constitutively activated receptor tyrosine kinases, e.g. EGFR, HGFR, IGFR, PDGFR, FGFR
- Inhibition of their intracellular effectors - non-receptor tyrosine kinases, e.g. RAS, JAK, STAT, PTEN-AKT signaling pathway
- Strategies targeting the transcription factor NFkB, by inhibiting proteasomes degrading its inhibitory subunit

3. **Apoptosis**

- Death receptor agonists
- Targeted induction of ROS
- Inhibition of the antiapoptotic protein Bcl-2
- Inhibition of HSP
- Induction of p53

4. **Invasion and metastasis of transformed cells**

- mAbs against integrins
- Inhibitors of matrix metalloproteases
- Inhibitors of receptor tyrosine kinases (FGFR, VEGFR, PDGFR)
- Inhibition of TGF-β signaling pathway

5. **Tumor neoangiogenesis**

- Interference with the VEGFR signaling pathway
- Application of recombinant and synthetic antiangiogenic factors (endostatin, thrombospodin)

Target molecules are (or will be in the future) therapeutically interfered with:

- Soluble receptors, reducing the effective concentration of humoral signals
- Monoclonal antibodies against the receptor or ATP-binding domain of tyrosine kinase receptors (Erbitux, Herceptin, etc.)
- Antagonists (tyrosine kinase inhibitors, e.g. Iressa, matrix-metalloprotease inhibitors)
- Antisense oligonucleotides
- RNA interference techniques (siRNA) directed against the expression of signaling molecules

Many of the above concepts are still at the level of experimental studies. Their future applicability is limited by several factors:

1. **Tumors are genetically heterogeneous**. Firstly, inter-individually, where a single nosological entity in different patients may have different pathogenetic mechanisms, but also within a single tumour, which contains different cell populations that may be differentially selected by treatment over time.
2. In addition to very early stage, where a single mutation may represent an 'Achilles heel' and therefore an ideal specific therapeutic target ('oncogene/pathway' addiction), the **genetic instability of a tumour** causes the accumulation of mutations leading to the promotion of an undesirable cellular programme. The transformed cell thus gains the advantage of compensating for therapeutic intervention at the level of a single signalling molecule or pathway.
3. Although targeted therapy represents a highly selective approach, there remains a **risk of adverse effects** both on-target (by interfering with the 'same signalling' of non-transformed cells) and off-target (by imperfect specificity and thus interference with other molecules).

The future lies in individualized treatment based on precise molecular diagnostics, targeting a specific patient, not just a nosological entity, using a rational combination of molecular targets ("multitargeting"), possibly in combination with other therapeutic modalities (surgery, radiation, etc.).

Links

Used literature

Lectures in biochemistry and pathobiochemistry and their study resources:

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