Elements of signal transduction as therapeutic targets in oncology

Basic characteristics of transformed cells and tumor formation and development:

- Ability to proliferate, reduced need for external pro-proliferative stimulation
- Resistance to apoptosis
- Ability to invasively grow and metastasize
- Evading immune surveillance
- The ability of neoangiogenesis

Cancer treatment options

Portfolio of concepts of the oncology treatment arsenal

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

Classical chemotherapeutic approaches can be divided into chemoprevention, "classical" chemotherapy that suppresses cell proliferation in different ways, epigenetic chemotherapy, hormonal treatment and induction of differentiation. A number of drugs used in these areas have been found through empirical approaches. They stop proliferation by acting on the level of transcription, translation, proteosynthesis or cell division itself.

For a rational approach to the treatment of cancer diseases, it is necessary to know the molecular essence of their pathogenesis and to find applicable specific molecular targets within them. Transformed cells form a minority population in most tumors, closely "collaborating" with cells of the tumor stroma (fibroblasts, vascular structures, cells of the immune system). 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 tumors

A conceptually new group of chemotherapy is represented by "targeted treatment" (so-called "targeted" or "designer therapy"). Unlike "conventional" chemotherapy, which, despite a certain degree of preference towards transformed cells, also affects other proliferating cell populations in the organism (bone marrow cells, epithelia, etc.), it is focused on molecules of signal-transduction pathways, characteristic of pathological proliferation or resistance to the apoptosis of tumor cells and to the oncogenetic processes induced by them. The ideal target of intervention is the tumor stem cell, which, unlike its more differentiated products, is capable of permanent self-renewal.

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

1. **Self-renewal of stem cells**
   - Telomerase inhibitors
   - Inhibition of gamma-secretase (Notch signaling pathway)
   - Inhibition of the Wnt-beta-catenin signaling pathway
   - Inhibition of the Sonic Hedgehog signaling pathway
2. **Proliferation / Cell cycle of progenitors**
   - 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
   - A strategy targeting the transcription factor NFkB, by inhibiting proteasomes degrading its inhibitory subunit
3. **Apoptosis**
   - Death receptor agonists
   - Targeted induction of ROS
   - Inhibition of the anti-apoptotic protein Bcl-2
   - HSP inhibition
   - 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 the TGF-β signaling pathway
5. **Tumor neoangiogenesis**
    - Intervention in the VEGFR signaling pathway
    - Application of recombinant and synthetic antiangiogenic factors (endostatin, thrombospodin)

Target molecules are (or will be) therapeutically targeted:

- 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
- By RNA interference (siRNA) techniques directed against the expression of signaling molecules

A number of the concepts mentioned above are still at the level of experimental studies. Their future usability is limited by several factors:

1. Tumors are genetically heterogeneous. On the one hand, inter-individually, when one nosological unit in different patients can have different pathogenetic mechanisms, but also within one tumor, which contains different cell populations, which can be differently selected by treatment over time.
2. Apart from the very early stage, when one mutation can represent an "Achilles heel" and therefore an ideal specific therapeutic target ("oncogene/pathway" addiction), the genetic instability of the tumor is the cause of the accumulation of mutations leading to the support of an unwanted cellular program. The transformed cell thus gains the advantage of compensation for the therapeutic intervention at the level of one signaling molecule or one pathway.
3. Although targeted therapy represents a highly selective approach, the risk of adverse effects both on-target (interfering with the "same signaling" of non-transformed cells) and off-target (imperfect specificity and therefore interference with other molecules) remains.

The future is individualized treatment, based on precise molecular diagnostics, focused on a specific patient, not only a nosological unit, using a rational combination of molecular targets ("multitargetting"), possibly in combination with other treatment modalities (surgery, radiation, etc.).

Sources

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