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Molecular targets for targeted radionuclide imaging and therapy in oncology

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Most modern drug therapies function by interaction with a defined molecular target that is present, often at enhanced levels. in the disease state for which the therapy is intended. The ability to image the levels of these targets before and after therapy and to interrogate the drug/target interaction is very important in drug development.

Molecular targeted radionuclide cancer therapy is also becoming of increasing importance, especially for disseminated diseases. Systemic chemotherapies often lack selectivity while targeted radionuclide therapy has important advantages as the radioactive cytotoxic unit of the targeting vector is specifically directed to the cancer, sparing normal tissues. The principle strategy to improve cancer selectivity is to couple therapeutic agents to tumour-targeting vectors. An advantage of using radiation instead of chemotherapeutics as the cytotoxic agent is the so called 'crossfire effect'. This allows sterilisation of tumour cells that are not directly targeted due to heterogeneity in target molecule expression or inhomogeneous vector delivery.

The aim is therefore to use as ligand-targeted diagnostic or therapeutic vectors coupled to either imaging (gamma or positron-emitting) or therapeutic (Auger-, alpha- and/or beta-emitting) radionuclides for either visualisation or therapy of the tumour. The properties of the molecular targets to which the ligands bind are fundamental for the achievement of this aim. It should be uniquely expressed, or at least highly overexpressed, on or in the target cells relative to normal tissues. The target should be easily accessible for ligand delivery and should not be shed or down-regulated after ligand binding. An important property of a receptor (or antigen) is its potential to be internalized upon binding of the ligand. This provides an active uptake mechanism and allows the therapeutic agent to be trapped within the tumour cells.

Molecular targets of current interest include:

Receptors: G-protein coupled receptors are overexpressed on many major human tumours. The prototype of these receptors are somatostatin receptors which show very high density in neuroendocrine tumours, but there are many other most interesting receptors to be applied for TRT. The targeting ligands for these receptors are radiolabelled regulatory peptides and their metabolically stabilised analogues.

Antigen epitopes

Antibodies, as unlabelled biological drugs, are becoming of increasing interest. They exert an antibody-dependent cellular cytotoxicity which leads to lysis of tumour cells. Radiolabelled versions of these (and other) antibodies are being developed worldwide. The disadvantage of the long circulating time of antibodies can be solved by engineering fragments such as diabodies, bivalent single chain variable fragments (scFv), minibodies or by pretargeting approaches.

Transmembrane transporters

Other interesting targets are transporters for radiolabelled amino acids and nutrients. Cancer cells require an increased supply of many such nutrients and obtain these by increased expression of some types of amino-acid transporter. A more detailed analysis of the relationship between amino-acid uptake and transporter expression in normal and malignant cells would be very valuable in identifying the clinical therapeutic potential of this class of tracer.

Tumour blood supply and extra-cellular matrix

Tumours require an efficient blood supply to grow and metastatise and active angiogenesis of new blood vessels is a feature of many tumours. Specific receptors expressed during this process represent a novel class of targets for TRT. The stroma that provides support for tumour growth and angiogenesis also contains many essential components that are upregulated in malignancy and represent a potential alternative to targeting the tumour cells themselves.

References

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