MOLECULAR TARGETS FOR TARGETED RADIONUCLIDE THERAPY

S. J. Mather

Barts and the London School of Medicine, UK
Email: s.j.mather@qmul.ac.uk

Molecular targeted radionuclide cancer therapy is 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. In targeted radionuclide therapy (TRT), the cytotoxic portion of the conjugates normally contains a therapeutic radiometal immobilised by a bifunctional chelator.

The aim is therefore to use as ligand-targeted therapeutics vectors coupled to Auger-, alpha- and/or beta-emitting radionuclides. 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. However, before the targeting ligands can be selected, the target molecule on the tumour has to be selected. 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: 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.

Extra-cellular matrix: Recently, another relevant class of target antigens has raised interest. Lectins, or carbohydrate binding proteins, recognize specific oligosaccharide structures on glycoproteins and glycolipids. It is well known that protein and lipid glycosylation are consistently altered in cancer cells for the aberrant activity of specific glycosyltransferase and glycosydases. Experimental evidence demonstrated that tumor growth and progression may depend, at least in part, on the presence of altered glycoproteins on the cell surface, which can mediate aberrant receptor-ligand interactions.