Molecular imaging for planning and monitoring treatment with targeted cancer drugs

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The aim of molecular imaging is to provide non-invasive tools to study the expression and function of biomolecules in patients. Molecular imaging may therefore be used to confirm the expression of drug targets and assess the heterogeneity of target expression between different lesions in individual patients. An example for this application is PET imaging of somatostatin receptor expression for planning of radionuclide therapy with Yttrium or Lutetium labeled somatostatin analogs. Development of specific imaging agents for drug targets is, however, a complex process, since in-vivo uptake of an imaging probes is not only determined by target expression, but also by multiple other factors including metabolic stability, blood clearance and unspecific binding. Therefore, the number of drug targets that can be imaged is still limited. Examples for drug targets that can be visualized clinically by molecular imaging include somatostatin, estrogen and androgen receptors as well as alpha-β integrins (1). Ligands for epidermal growth factor receptors (EGFR) and vascular endothelial growth factor (VEGF) are in preclinical development (1).

Another application of molecular imaging is monitoring the effects of targeted drugs. For example, src kinase inhibition has recently been shown in preclinical studies to inhibit the function of the alpha-β integrin leading to decreased migration and proliferation of glioma cells (2). A series of recent studies has now indicated that oncogene activation (e.g. c-myc) or loss of tumour suppressor genes (e.g. p53) causes activation of glycolysis as well as of glutamine and lipid metabolism (3-7). This suggests that imaging of tumour metabolism may provide a new approach for monitoring the inhibition of oncogenic signaling pathways by targeted drugs. In patients with gastrointestinal stromal tumours, FDG uptake decreases within hours after treatment with the c-kit inhibitor imatinib. Experimental studies have suggested that this rapid reduction of glucose metabolic activity does not reflect cell death, but a translocation of glucose transporters from the plasma membrane to the cytosol (8). Similarly, inhibition of mTOR kinase with rapamycin has been shown to result in decreased glucose metabolic activity of glioma cells in-vitro as well as in animal models (9). Since imaging probes for glucose, amino acid and lipid metabolism are clinically available, PET with these metabolic imaging probes could readily be integrated in clinical trials of new targeted drugs.

References