Proliferation Markers for the Differential Diagnosis of Tumor and Inflammation

A. van Waarde (Groningen) and P. Elsinga (Groningen)

FDG, the most common radiopharmaceutical for PET imaging in oncology, is not tumor-specific. This analog of glucose is known to accumulate in viral, bacterial and fungal infections and in other forms of inflammatory tissue. Strong FDG accumulation can also occur in brown fat, particularly in young subjects at low environmental temperature. FDG accumulation in inflammatory tissue may result in false positives during cancer screening and in false classification as a nonresponder during anti-tumor therapy. Yet, discrimination between benign and malignant processes is often possible when the kinetics of FDG uptake is taken into account (e.g., by delayed, dual or dynamic PET imaging).

Other PET tracers which are considered as proliferation markers may allow an improved differential diagnosis of tumor and inflammation. These include amino acids, nucleosides, choline derivatives, receptor ligands, antibodies and antibody fragments. Strictly speaking, only labelled nucleosides which are incorporated into DNA (e.g., 2-11C-thymidine, 2Br-brmofluorodeoxyuridine, 11C-FMAU) are true proliferation markers, but the tissue kinetics of radiopharmaceuticals tracing amino acid transport, membrane metabolism, enzyme activity or receptor expression can be a surrogate marker of cellular proliferation if the activity of such processes is increased in rapidly dividing cells.

Well-known imaging targets for oncology are: (i) glucose transport via the GLUT1 carrier (18F-FDG); (ii) amino acid transport (11C-methionine, O-2-[18F]fluoroethyl-L-tyrosine); (iii) choline kinase activity (11C-choline); and (iv) activity of thymidine kinase 1 (18F-FLT). Less-characterized targets are sigma, opioid, peptide (e.g. bombesin, or VIP), and epidermal growth factor receptors. Only limited information is available on the tumor specificity of PET probes for these targets. Nucleosides such as 18F-FLT, amino acids, and choline derivatives have been reported to be more tumor-specific than 18F-FDG, both in experimental animals and in humans. However, the specificity of such tracers is not absolute.

11C-Methionine can show high uptake in brain abscesses. 11C-choline has been found to accumulate strongly in bacterial infections and in turpentine-induced inflammatory tissue. 18F-FLT can be taken up in non-metastatic reactive lymph nodes because of reactive B-lymphocyte proliferation. Moreover, FLT-PET may not distinguish between benign lesions showing blood-brain barrier disruption and malignant brain tumors. Although sigma receptor ligands are not accumulated in turpentine-induced inflammation in rodents, these radiopharmaceuticals may bind to certain elements of the immune system (e.g., lymphocytes).

Because of such limitations, the tumor specificity of PET will never reach 100%. Each radiolabeled proliferation marker (or surrogate marker of proliferation) has high physiological uptake in some areas of the body and the tumor uptake of these radiopharmaceuticals is often lower than that of FDG. Proliferation markers should therefore not be considered as a replacement of FDG, but rather as useful additions to the imaging arsenal which can provide additional diagnostic specificity and biological information for treatment planning and response monitoring.

References