Leading article

Cellular and molecular imaging of the arteries in the age of precision medicine

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Cellular and molecular imaging techniques use cell-specific or process-specific imaging probes to identify and assess biological activity. MRI and combined PET–CT are the current main techniques. PET–CT has been used to identify metastases for many years. This established technique is being adapted for use in other clinical domains, such as cardiovascular disease, where molecular and cellular imaging techniques have the potential to improve diagnosis, risk stratification and management.

MRI offers high spatial resolution, avoids ionizing radiation and results in excellent soft tissue contrast, although it is not suitable for all patients because of issues such as claustrophobia or the presence of implanted metallic devices. Paramagnetic MRI agents, such as gadolinium, are widely used to delineate morphological features of disease such as blood pool, thrombus and fibrosis. More recently, nanoparticles have been used as smart cellular contrast agents that give an added dimension to MRI. Ultrasmall superparamagnetic particles of iron oxide (USPIOs), such as ferumoxytol, are taken up actively by tissue-resident macrophages and allow visualization of cellular tissue inflammation. They have been used to image acute myocardial infarction, carotid artery disease, abdominal aortic aneurysms (AAAs) and solid organ transplantation.

In contrast to MRI, PET has low spatial resolution and does expose the patient to ionizing radiation, but is highly sensitive and can detect very small areas of biological activity. It relies on the incorporation of positron-emitting radionuclides (often ^{18}F or ^{11}C) into molecules of interest, such as fluorodeoxyglucose, so that metabolic or biological activity can be detected and tracked. To overcome the low spatial resolution of PET, images are often obtained on a hybrid scanner where PET images are fused with structural images obtained from CT (PET–CT) or MRI (PET–MRI).

Predicting the progression of vascular disease managed conservatively is challenging. However, if biological events could be identified that precede clinical events, then interventions could be targeted more appropriately to individual patients.

Accurate prediction of AAA growth rate is difficult, as many aneurysms exhibit staccato growth[1]. USPIO-enhanced MRI has been used to assess cellular inflammation in AAA where it may predict disease progression and outcomes. This finding is not independent of models incorporating clinical risk factors including aneurysm diameter and smoking status[2]. More recently, PET–CT of AAA has demonstrated that [^{18}F]sodium fluoride uptake (which highlights areas of microcalcification, necrotic inflammation and loss of tissue integrity[3]) is a predictor of aneurysm growth and need for repair, independent of clinical risk factors for progression[4]. These data demonstrate the potential of novel imaging techniques to evaluate AAA growth rates.

The main indicator for treatment of symptomatic and asymptomatic carotid disease is the severity of carotid stenosis. However, [^{18}F]sodium fluoride PET–CT can highlight phenotypically high-risk carotid plaque in patients who have recently had a transient ischaemic attack or stroke[5]. This could be used to select patients who may benefit most from carotid surgery. [^{18}F]Sodium fluoride uptake also correlates with vascular inflammation in the lower limb[6] and ongoing studies are investigating the use of PET–CT to predict severe limb ischaemia.

Vascular surgery causes major physiological stress, with up to one in five patients experiencing perioperative myocardial injury or infarction associated with an increased risk of death. Preclinical and clinical studies have demonstrated that myocardial infarction destabilizes remote atherosclerotic plaque[7], leading to new ischaemic events[8]. Acceleration of inflammation in atherosclerotic plaque remote to the surgical field may be associated with adverse postoperative cardiovascular events. Current preoperative risk prediction strategies are limited by poor positive predictive values[9]. In future, systemic inflammation could be evaluated before surgery using cellular or molecular imaging, to provide a personalized assessment of perioperative risk.

Cellular and molecular imaging techniques are also being used as outcome measures in drug trials, allowing early evaluation of therapeutic effects on vessel biology that would otherwise take much longer to manifest as clinical events. In the ATHEROMA (Atorvastatin

Therapy: Effects on Reduction of Macrophage Activity) study, Tang and colleagues[10] used USPIO-enhanced MRI to quantify changes in vessel wall inflammation following high-dose statin treatment in patients with carotid artery disease, and found that aggressive lipid-lowering therapy was associated with a reduction in inflammation at 3 months. [^{18}F]Sodium fluoride PET–CT is currently under investigation as an outcome measure in studies of coronary artery disease and aortic stenosis.

In the age of precision medicine, a top priority is the search for new ways to predict vascular disease progression[11]. Cellular and molecular imaging biomarkers have the potential to contribute towards individualized prediction of cardiovascular disease progression, personalized intervention and monitoring of therapeutic drug effects. The greatest limitations of these techniques are availability, expense and expertise. However, [^{18}F]fluorodeoxyglucose PET–CT is used widely in oncology, and fluorine-based tracers are easy to manufacture and are stable enough to be transported some distance to other centres without manufacturing capabilities.

This is a rapidly evolving area with many new techniques and tracers emerging. Novel hybrid PET–MRI scanners allow simultaneous superior soft tissue resolution and multiparametric imaging with reduced radiation exposure. Novel PET tracers have the potential to target more specific biological processes; some have already been used in preclinical studies. For example, ^{18}F-radiolabelled NOTA-RGDfK binds to integrin receptors and has a high affinity for $\alpha_v\beta_3$, which is expressed at low levels on quiescent cells but is highly upregulated on activated vascular macrophages and in states of angiogenesis. It could be a potentially useful imaging probe in AAA disease. Another $\alpha_v\beta_3$ radiotracer, [^{18}F]fluciclatide, has been used to identify areas of functional recovery of the myocardium following infarction, and one autoradiography study[12] demonstrated that [^{18}F]fluciclatide detects areas of angiogenesis in AAA *in vitro*. [^{11}C]PK11195 binds selectively to the translocator protein, which is highly expressed by macrophages, and can identify vascular inflammation in the carotid arteries[13], but has yet to be applied in other vascular diseases.

Disclosure

The authors declare no conflict of interest.

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