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In vivo imaging for stem cell therapy: new developments and future challenges

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> "To deride the hope of progress is the ultimate fatuity, the last word in poverty of spirit and meanness of mind."[1]
>
> Paul Berg

In recent years, the ground-breaking field of stem cell-based regenerative medicine has been throwing up the tantalising prospect of potential new therapies for a range of diseases. Adult, autologous stem cells have already been tested in early-phase clinical trials in humans and in some cases are now being examined in longer-term clinical trials. Meanwhile, potential therapies based on embryonic stem cells and induced pluripotent stem cells (reprogrammed differentiated somatic cells) are still in the basic research phases; their translation to human diseases will depend on the adequate addressing of crucial issues, such as the risk of mutagenesis and malignant transformation. Furthermore, the clinical translation, to humans, of techniques shown to be suitable in animal models of disease may encounter hurdles beyond simple biocompatibility issues. Challenges to be overcome are related, among other things, to the high cost of these techniques, their applicability in acute conditions, ethical concerns over the use of embryonic cells and the need for regulatory approval[2].

There also remain important unanswered questions regarding the engraftment, viability, biology and safety of transplanted stem cells, as well as the feasibility of correlating organ functional information with their presence/absence in the living subject. These are questions that can be addressed through the use of non-invasive imaging of transplanted stem cells in the living subject. Indeed, non-invasive molecular imaging strategies are destined to play an increasingly critical role as the different regenerative therapies are tested for clinical use. Such imaging data can potentially shed light on the interaction of exogenous stem cells with the host organism and provide answers to questions such as the best cell type(s), timing of delivery, dose and delivery route to use.

The ideal imaging modality, which will have excellent spatial resolution and molecular sensitivity, should be able to guide the delivery of cells and should serially monitor stem cell fate. Currently, however, no such imaging modality exists. The use of direct labelling, with compounds such as iron oxide or [^{18}F]fluorodeoxyglucose, is hindered by concerns that the label may become dissociated from the exogenous stem cell and that this approach may thus not be a reliable means of monitoring long-term cell viability.

Conversely, these techniques continue to be a valid method for determining the immediate success of stem cell delivery. Reporter gene imaging, meanwhile, is a non-invasive means of determining stem cell viability and of studying transplanted cell biology.

Ultimately, the choice of modality depends on the question being addressed. If the objective of the study is to image the delivery and short-term homing of stem cells in different organs, a direct labelling approach may be the answer, even though any potential toxicity must be taken into account. MRI provides the highest spatial resolution and near real-time image guidance for cell delivery, albeit with significantly lower molecular sensitivity than other modalities, such as PET or SPECT. If, instead, long-term monitoring of stem cell viability is the objective, reporter gene imaging, using PET or SPECT, appears to be a better option[3].

In the next section, focus will be placed on new developments in cell therapy imaging. Subsequently, the neural and cardiac systems will be used as examples of novel applications of more established imaging strategies.

Recent methodological developments in cell therapy imaging

The open issues and current applications of cellular imaging in regenerative therapy are here illustrated through a brief look at some of the most recently reported investigations.

Exposure of cells and tissues to high magnetic fields is the functional principle of MRI, which has been established as an efficient means of detecting mesenchymal stem cells (MSCs) labelled with superparamagnetic particles of iron oxide (SPIO). Despite initial reports that SPIO labelling of MSCs is safe and does not affect MSC biology, recent studies indicate that the procedure can affect the metabolism and function of these cells. The effects of magnetic fields on unlabelled and labelled human MSCs were recently explored through migration assays, quantification of colony-forming units, analyses of gene and protein expression, and analyses of MSC proliferation capacity, viability and differentiation potential.[4] It was found that human MSCs labelled with SPIO permanently exposed to magnetic fields were arranged and grew according to the magnetic flux lines. SPIO-labelled MSCs exposed to magnetic fields showed a significantly enhanced total iron load per cell (TIL) compared to SPIO-labelled MSCs not exposed to magnetic fields, exposure thus being found to result in optimised imaging properties (detection limit: 1,000 MSCs). In terms of TIL and imaging properties, exposure to magnetic fields immediately after labelling proved superior to exposure 24 h after labelling. On a functional level, exposure to magnetic fields inhibited the colony-forming ability of labelled MSCs and led to enhanced expression of lipoprotein lipase and peroxisome proliferator-activated receptor-gamma in labelled MSCs under adipogenic differentiation, and to reduced expression of alkaline phosphatase in unlabelled MSCs undergoing osteogenic differentiation, as detected by qRT-PCR. Moreover, microarray analyses revealed that exposing labelled MSCs to magnetic fields led to an upregulation of CD93 mRNA and cadherin-7 mRNA and to a downregulation of zinc finger FYVE domain mRNA. Exposure of unlabelled MSCs to magnetic fields led to an upregulation of CD93 mRNA, lipocalin-6 mRNA, sialic acid acetylesterase mRNA and olfactory receptor mRNA, and to a downregulation of ubiquitin-1 mRNA. No influence of exposure to magnetic fields was observed on the migration capacity, viability, proliferation rate or chondrogenic differentiation capacity of labelled or unlabelled MSCs. In this study both SPIO and the static magnetic field were identified as independent factors affecting the functional biology of human MSCs. The authors conclude that further in vivo investigations will elucidate the molecular mechanisms underlying the interaction of magnetic fields with stem cell biology. Studies like this one underscore the importance of evaluating not only the imaging aspect (when evaluating an imaging study), but also whether the technique chosen impacts (positively or negatively) on the therapeutic strategy being evaluated.

Advances in the study of cell biology and its interaction with the host microenvironment also depend on the development of improved techniques for the non-invasive imaging of protein--protein interactions (PPIs). Massoud et al. molecularly engineered a PET-based split reporter (herpes simplex virus type 1 thymidine kinase), cleaved between Thr265 and Ala266, and used it in a protein-fragment complementation assay (PCA) to quantify PPIs in mammalian cells and to image them by microPET in living mice[5]. An introduced point mutation (V119C) markedly enhanced thymidine kinase complementation in PCAs, on the basis of rapamycin modulation of FKBP12-rapamycin-binding domain (FRB) and FKBP12 (FK506 binding protein), the interaction of hypoxia-inducible factor-1alpha with the von Hippel--Lindau tumour suppressor, and an oestrogen receptor intramolecular protein-folding assay. As the authors point out, applications of this unique split thymidine kinase are potentially far-reaching. By allowing fully quantitative and tomographic PET localisation of PPIs in preclinical small- and large-animal models of disease, it could, for example, allow considerably more accurate monitoring of immune and stem cell therapies.

The chemokine receptor CXCR4 and its cognate ligand CXCL12 are crucial in establishing the presence of metastases from many tumour types. Earlier this year a report was published evaluating the use of [^{64}Cu]AMD3100, a positron-emitting analogue of the stem cell-mobilising agent plerixafor, developed to image CXCR4 in human tumour xenografts preselected for graded expression of this receptor[6]. This imaging method was evaluated in lung metastases derived from human MDA-MB-231 breast cancer cells. Ex vivo biodistribution studies, performed to validate the in vivo imaging data, confirmed the ability of [^{64}Cu]AMD3100 to image CXCR4 expression. The findings of this study thus demonstrate the feasibility of imaging CXCR4 by PET using a clinically approved agent as a molecular scaffold and illustrate how novel molecular imaging can be used to monitor the success of a specific therapy, by targeting/imaging a specific characteristic of a tumour cell. A similar strategy could be used in the field of cell therapy, once specific cell phenotypes have been identified.

Ultrasound is a modality commonly used for assessment of cardiac function, but his role in stem cell monitoring has been limited. Recently, Kuliszewski et al (cardiovascular research 2009) developed a reporter gene, whose expression results in a cell surface marker (H-2kk) that can be monitored using ultrasound labelled microbubbles. In their validation study, the authors incorporated the H-2kk reporter gene in rodent EPCs and deliver cells in a scaffold matrix. Although receptor based strategies are less sensitive (as opposed to enzyme based systems) and ultrasound is les sensitive than nuclear techniques, this approach the possibility of using ultrasound-based reporter genes to monitor transplanted cells.

Imaging of cell therapy as a repair mechanism in neurological disease

As was pointed out in a recent paper, neural stem cells (NSCs) are defined by their ability to self-renew, to differentiate into cells of all glial and neuronal lineages throughout the neuraxis, and to populate developing or degenerating central nervous system (CNS) regions[7]. The recognition that NSCs propagated in culture can be re-implanted into mammalian brain, where they might integrate appropriately throughout the mammalian CNS and stably express foreign genes, has unveiled a new role for neural transplantation and gene therapy, and possibly a new strategy for addressing the CNS manifestations of diseases previously refractory to intervention. However, the mechanisms by which stem cell transplants induce functional recovery are yet to be elucidated.

Recently, the efficacy of human (h) NSCs derived from human embryonic stem cells and the mechanisms enhancing brain repair were recently explored in a rat model of neonatal HI brain injury[8]. hNSCs, genetically engineered for in vivo molecular imaging, were

transplanted twenty-four hours after the induction of HI and their survival was monitored using Bioluminiscence imaging (BLI). The transplanted HI brain injury animals showed significant improvements in their use of the contralateral impeded forelimb and in their performance on the Rotorod test. The grafts showed good survival, dispersion and differentiation, with an increase in uniformly distributed microglia cells was observed on the grafted side. Anterograde neuroanatomical tracing demonstrated significant contralesional sprouting, with upregulation of genes involved in neurogenesis, gliogenesis and neurotrophic support. These results suggest that hNSCs transplants enhance endogenous brain repair through multiple mechanisms in response to HI brain injury and that the location and survival can be monitored non-invasively.

Neural stem cells reside in two major niches in the adult brain [i.e. the subventricular zone (SVZ) and the dentate gyrus of the hippocampus], which can be mobilised by insults like cerebral ischaemia. According to recent studies, the brain's own regenerative capacity can be enhanced by pharmacologically-induced expansion of the endogenous NSC niches. Novel therapeutic approaches of this kind need to be evaluated through longitudinal and individual monitoring of these niches. As recently reported, this can be done using a PET direct labelling strategy to monitor the uptake of 3′-deoxy-3′-[^{18}F]fluoro-l-thymidine ([^{18}F]FLT) by endogenous NSCs in the normal and diseased adult rat brain in vivo[9]. This method indeed allowed visualisation of NSC niches in the living rat brain, identified as increased [^{18}F]FLT binding in the SVZ and the hippocampus. Importantly, local cerebral ischaemia and subsequent blood--brain barrier damage did not interfere with the capability of [^{18}F]FLT -PET to visualise NSC mobilisation. Moreover, [^{18}F]FLT-PET allowed in-vivo quantification of increased NSC mobilisation caused by pharmacological stimulation or by focal cerebral ischaemia. These data suggest that non-invasive longitudinal monitoring and quantification of endogenous NSC activation in the brain is feasible and that [^{18}F]FLT-PET could be used to monitor the effects of drugs aimed at expanding the NSC niche.

In another very recent study, the safety and efficacy of Schwann cells induced from MSCs as a source for auto-cell transplantation therapy in nerve injury was recently investigated in a cynomolgus monkey peripheral nervous system injury model[10]. Serial treatment of monkey bone marrow stromal cells (BMSCs) with reducing agents and cytokines induced their differentiation into cells with Schwann cell properties at a very high ratio. Expression of Schwann cell markers was confirmed by both immunocytochemistry and reverse transcription-polymerase chain reaction. Induced Schwann cells were used for auto-cell transplantation into the median nerve and monitored for 1 year. No abnormalities were observed in general conditions. Ki67-immunostaining revealed no sign of massive proliferation inside the grafted tube. Furthermore, [^{18}F]FDG-PET scanning demonstrated no accumulation of radioactivity except in regions where accumulation is physiological. Restoration of the transplanted nerve was corroborated by behavioural analysis, electrophysiology and histological evaluation. The results of this study suggest that auto-cell transplantation therapy using BMSC-derived Schwann cells is safe and effective for accelerating the regeneration of transected axons and for promoting the functional recovery of injured nerves. The practical advantages of BMSCs are expected to render this system applicable in spinal cord injuries and other neurotraumas or myelin disorders in which acceleration of regeneration can be expected to enhance functional recovery.

Since efforts to develop cell therapies are ultimately geared at finding clinical applications, it is important for non-invasive cell therapy monitoring in animal models to be adaptable to humans. Cytolytic T cells (used for treatment of advanced glioma) were recently transfected with the mutant version of the herpes simplex virus type 1 (HSV1-sr39tk) reporter gene and delivered to patients with advanced glioma. After administration of 9-[4-[^{18}F]fluoro-3-(hydroxymethyl)butyl]guanine ([^{18}F]FHBG), PET imaging was performed. The great

importance of this work lies in the fact that it is the first study of reporter gene imaging in cell therapy in humans, and will “pave the way” for other similar studies that will optimise these techniques.[11]

These representative studies illustrate the broad-spectrum potential of non-invasive monitoring and assessment of transplanted cells. As seen with other systems, these technologies will probably be integrated with other assessment tools already available (and even already applied clinically).

Imaging of cell therapy for myocardial repair

There is growing interest in the clinical application of stem cell-based therapy as a novel approach to the treatment of acute myocardial infarction (MI)[12]. After all, as recently remarked by Smits et al.[13], current treatments cannot prevent the loss of cardiac contractility caused by cardiomyocyte death, and therefore patients that do survive MI are prone to develop progressive impaired cardiac function, which may lead to heart failure. It has been suggested that cell-based therapy could prevent progression to end-stage heart failure by (re)generating contractile tissue in the damaged heart. In recent years, the cardiomyogenic differentiation capacity of many different cell sources has been extensively studied, both in vitro and in vivo. Promising pre-clinical studies led to Phase I/II clinical trials, but with conflicting results. As mentioned above, variables like dose, timing and cell type remain unclear and are focus of active investigation. Molecular imaging approaches will be important for upcoming studies that will focus on these issues.

The transplantation of stem cells derived from human subcutaneous adipose tissue (hASCs) for cardiac regeneration is a promising therapeutic approach due to the proliferation and differentiation capacity of these cells. Understanding the fate of injected hASCs would help to understand how they work in vivo. A recently published study set out to track the long-term fate, including survival, differentiation, proliferation, apoptosis, migration and growth factor secretion, of intramyocardially injected hASCs following experimental acute MI in an immunodeficient mouse model[14]. Myocardial infarction was experimentally induced in severe combined immunodeficient mice by permanent ligation of the left anterior descending coronary artery. Lentivirally labelled hASCs [5×10^5; expressing green fluorescence protein (GFP) and luciferase] were injected into the peri-infarct region. Colony formation, growth kinetics and differentiation of transduced hASCs were analysed in vitro and compared to those of control hASCs. The survival and migration of the injected hASCs were tracked by luciferase-based bioluminescence imaging for 10 weeks. Immunofluorescence and terminal deoxynucleotidyl transferase dUTP nick end labelling staining were used to assess differentiation, proliferation, growth factor expression and apoptosis of grafted hASCs in infarcted hearts and potential distribution to other tissues.

Lentivirus transduction and GFP and luciferase expression were not found to influence proliferation or differentiation of hASCs. Bioluminescence imaging demonstrated that injected hASCs survived in infarcted hearts during the 10-week follow-up. Immunofluorescence imaging confirmed that hASCs engrafted in ischaemic hearts expressed bFGF and IGF-1, and did not migrate to other organs. Of all engrafted hASCs, 3.5% differentiated into cardiomyocytes or endothelial cells. Other cells maintained their proliferative potential or underwent apoptosis. It was concluded that luciferase-based bioluminescence imaging allows long-term tracking of intramyocardially injected hASCs in living mice. The hASCs might enhance the function of injured hearts through long-term engraftment, growth factor secretion and trans-differentiation to cardiomyocytes and endothelial cells.

As mentioned previously, there is considerable interest in identifying the biological factors that may increase transplanted cell functionality. In this regard, it has been suggested that vascular endothelial growth factor (VEGF) and statins enhance the survival, proliferation and function of endothelial progenitor cells (EPCs). The following study was conducted to investigate whether reporter gene PET can be used to detect the effects of atorvastatin and VEGF on survival of EPCs after transplantation in the rat heart[15]: Healthy nude rats received an intramyocardial injection of 4 million human EPCs retrovirally transduced with the sodium/iodide symporter gene for reporter gene imaging. Reporter gene expression was imaged at days 1 and 3 after injection on a small-animal PET scanner with iodine-124, and the presence of EPCs was confirmed by immunohistochemistry with human CD31 antibodies. The control group received EPCs transduced only with the reporter gene, whereas the treatment groups received oral atorvastatin (10 mg/kg/day) and EPCs co-transduced with adenoviral vectors encoding VEGF in addition to sodium/iodide symporter. Immunohistochemistry showed more EPCs at the site of injection after atorvastatin treatment and in the presence of VEGF expression in EPCs than in controls. PET successfully visualised EPCs as focal with iodine-124 accumulation at the site of injection. The amount of iodine-124 accumulation assessed by PET was significantly higher in the pretreatment than in the control group. Autoradiography confirmed iodine-124 accumulation in the myocardium that correlated with the number of EPCs. On the basis of these findings, it can be concluded that early survival of transplanted EPCs in the rat myocardium is prolonged by pretreatment with a combination of atorvastatin and VEGF. Reporter gene PET, by successfully quantifying the effect, emerged as an attractive tool for monitoring stem cell survival in vivo.

The success of stem cell transplantation for cardiac regeneration is partially limited by low retention/engraftment of the delivered cells. A clinically applicable method for accurate quantification of cell retention would allow optimisation of cell delivery. In an attempt to quantify acute myocardial retention of cardiac-derived stem cells (CDCs) and evaluate different delivery methods with PET[16], CDCs were derived from syngeneic, male Wistar Kyoto (WK) rats, labelled with ^{18}F-FDG and injected intramyocardially into the ischaemic region of female WK rats after permanent left coronary artery ligation. The effects of fibrin glue (FG), bradycardia (adenosine) and cardiac arrest were examined. Imaging with ^{18}F-FDG-PET was performed for quantification of cell retention. Quantitative PCR for the male-specific SRY gene was performed to validate the PET results. Myocardial retention of cells suspended in phosphate-buffered saline 1 h after delivery was 17.6% by PCR and 17.8% by PET. When CDCs were injected immediately after induction of cardiac arrest, retention was increased to 75.6%. Adenosine slowed the ventricular rate and doubled CDC retention (35.4%). A similar increase in CDC retention was observed after epicardial application of FG at the injection site (37.5%). The PCR showed a significant increase in 3-week cell engraftment in the FG-treated animals (22.1% and 5.3% for FG and phosphate-buffered saline, respectively). These results demonstrate that in vivo PET (using a direct labelling approach) allows accurate measurement of CDC retention early after intramyocardial delivery. Furthermore, they provide evidence that sealing injection sites with FG or lowering ventricular rate with adenosine might be clinically translatable methods for improving stem cell engraftment in a beating heart.

Transplantation of human endothelial progenitor cells (hEPCs) may improve vascularisation and left ventricular function after myocardial infarction. In a study exploring whether cross-linking of EPCs enhances the deposition of cells in the rat heart after clinical-like, intracoronary transplantation[17], [^{111}]In-oxinate-labelled hEPCs were infused by a minimally invasive technique into the coronary arteries of immunosuppressed Wistar rats under control conditions and after ischaemia/reperfusion. In a second set of experiments hEPCs were treated with phytohaemagglutinin to create small cell clusters prior to transplantation.

Continuous three-dimensional HiSPECT images for 1 h and after 48 h revealed that cell deposition was significantly higher when hEPCs were cross-linked. Therefore, cross-linking of hEPCs appears promising as a means of increasing, also in a clinical setting, the number of trapped cells.

As the possible clinical applications of stem cell therapy grow wider, it is becoming crucial to optimise strategies for monitoring its success, first in large-animal models of disease and then in humans. Imaging of MSCs was recently shown to be possible in a swine model. In this study, porcine MSCs were transfected, albeit transiently, using an adenoviral vector, with the HSV1-sr39tk driven by the cytomegalovirus promoter, and delivered to the anteroseptal myocardium. After the intravenous delivery of the PET substrate [^{18}F]FHBG, the authors performed PET scanning and were able to localise and quantify the PET signal, as a surrogate of the number of viable cells. This study is important as it constitutes the first demonstration of stem cell imaging with reporter genes in a large-animal model, and thus brings closer the transition to human use[18].

Conclusions

Regenerative medicine encompasses “tissue engineering”, the in vitro fabrication of tissues and/or organs using scaffold material and viable cells, and “cell therapy”, the in vivo transplantation or manipulation of cells in diseased tissue[19]. In almost any organ system, tissue engineering strategies are likely to involve some combination of cell therapy and scaffolding engineering. However, for these therapies to be optimised it is becoming crucial to gain a better understanding of their behaviour directly in the living subject.

Molecular imaging allows the non-invasive visualisation of cellular and molecular processes in living subjects. As others have remarked[20], for cell-based therapy to truly succeed, we have to be able to track the progress of delivered cells, establish the duration of cell survival, and monitor any potential adverse effects. The insights gathered from basic research imaging studies will yield valuable insights allowing better design of clinical trials. In this scenario, even though current imaging tools have shed light on different aspects of stem cell biology in vivo, stem cell biologists and imaging experts need to step up their efforts to develop, validate and accelerate progress in this field. Stem cell tracking requires high sensitivity and high spatial resolution; at present, no single imaging modality is perfect in all respects. Efforts now should focus on the development of multimodality imaging approaches able to answer biologically relevantquestions and promote the clinical translation of these techniques.

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