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Molecular Imaging of Stem Cells: A New Area for Neuroscience

Nora Sandu[1,2], Fatemeh Momen-Heravi[3], Pooyan Sadr-Eshkevari[4], Ali Arvantaj[5] and Bernhard Schaller[2]

[1]*Department of Neurosurgery, University of Lausanne, Lausanne,*
[2]*Department of Neurosurgery, University of Paris 7, Paris,*
[3]*Craniomaxillofacial Research Center, Shariati Hospital, Tehran University of Medical Sciences*
[4]*Dental Section, Farzan Clinical Research Institute, Tehran,*
[5]*Department of Neurology, Baylor College of Medicine, Houston,*
[1]*Switzerland*
[2]*France*
[3,4]*Iran*
[5]*USA*

1. Introduction

Nowadays, new imaging modalities such as molecular imaging have enabled both practitioners and researchers to visualize, trace and measure biological processes at the level of cells or even single molecules. Instruments of nuclear medicine, like Positron Emission Tomography (PET), Single-Photon Emission Computed Tomography (SPECT) and gamma scintigraphy have largely contributed to the evolving and promising era of personalized medicine. Such recently introduced molecular imaging techniques take advantage of an additional potential for broad application in imaging molecular or cellular events in vivo: gene/protein function and regulation, signal transduction, transcriptional regulation and characterization of transgenic animals (Jacobs et al., 2003). Most importantly, molecular imaging will render possible the identification of potential molecular therapeutic targets, in the development of new treatment strategies, and in their successful implementation into clinical application (Jacobs et al., 2003). As a description, molecular imaging is a process of getting signals originating from live organisms after the administration of specific agents that target specific markers found at tissue or cellular level. Such nuclear imaging is the most well-known instrument of all molecular imaging methods and has been set as the gold standard.

In this chapter, the authors will discuss PET and other more recent molecular imaging techniques such as near infrared fluorescence (NIRF). Moreover, we will put emphasis on the application of molecular imaging in visualization of stem cell transplantation as a ground breaking treatment modality for neurodegenerative and other neurological diseases. The authors stand among the very first who has implemented recently introduced molecular imaging techniques into experimental research and clinical practice.

2. Cell therapy

Cell therapy, as a promising method using live components of human tissue for treatment of neurological diseases, is one of the mainstays of the wide field of regenerative medicine.. Among stem cell sources available up to date, mesenchymal stem cells (MSCs) have generated a great deal of interest because of their potency in terms of regeneration and tissue engineering (Wislet-Gendebien et al., 2012).

Neurodegenerative disease is a term which encompasses a wide range of acute and chronic neurological diseases such as Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS), Alzheimer's disease, multiple sclerosis (MS), stroke, and spinal cord injury. Because of the fact that central nervous system reveals limited capacity of regeneration and tissue replacement, cell therapy and tissue regeneration of injured or degenerated tissue, as a potential new therapeutic modality, draws lots of attention (Wislet-Gendebien et al., 2012). Stem cells have the potential to differentiate into many different cell types. Recent research has concerned an exciting opportunity to apply MSCs especially in the management of neurodegenerative diseases, because of their potential to differentiate into neurons (Lee et al., 2010).

It has been shown that the injection of MSCs could be profitable in the treatment of neurodegenerative diseases such as Parkinson's disease (Levy et al.), Spinal Stroke and cerebral ischemia (Sieber-Blum, 2010), Alzheimer's disease (Lee et al., 2010), Multiple Sclerosis (Grigoriadis et al., 2011), Huntington's Disease (Snyder et al., 2010). The advantages of using stem cells for regenerative medicine are not only the eases of harvesting from bone marrow or other donor sites but also the minimal risk of tissue rejection because of the application of autologous cells.

Interestingly, recent data suggest that intravenously injected MSCs could migrate into the brain and pass blood-brain barrier (BBB), which is basically formed by brain microvascular endothelial cells (BMECs), and restrict the passage of immune cells and different molecules into the brain. The exact mechanism of this phenomenon, whether it is based on Integrin-mediated adhesion or is matrix metalloproteinase dependent extracellular matrix degradation, is yet not clear (Krampera et al., 2007, Matsushita et al., 2011).

One of the main clinical problems of stem cell transplantation is the difficulty of detection, localization, and examination of the stem cells in vivo at both cellular and molecular levels (Sandu et al.). State-of-the-art molecular imaging techniques provide new superior means of noninvasive, repeated, and quantitative tracking of stem cell implants or transplants (Sandu et al.). From initial deposition to the survival, migration, and differentiation of the transplant/implanted stem cells, current molecular imaging methods allow monitoring of the infused cells in the same live recipient bed over time (Sandu et al.).

3. Positron Emission Tomography (PET)

Over the past two decades, PET has been introduced and applied widly in the milieu of diagnosis including head and neck diseases. Along with a growing interest to use PET in tracing different types of molecules such as amino acids, receptor ligands, glucose and other metabolic substrates which follow specific metabolic pathways have been utilized to assess

different tissue functions, especially in neoplasms (Cornelius et al., 2011). The main substances for radio-labeling are fluorine-18 (F), gadolinium-68 (Ga) and Carbon-11 (C). The advantages that they confer upon other positron emitting isotopes such as O, N and C are their longer half-life time which results in superior tissue distribution and consequently a dynamic imaging of higher accuracy (de Langen et al., 2008, Keiding et al., 2010, Floeth et al., 2011, Henze et al., 2005).

Among metabolic substrates, F-fluorodeoxyglucose is the most renowned molecular tracer in oncology. It has been shown that F-FDG uptake may increase in neoplasmic cells which are believed to be indicative of an increased glycolysis and a subsided respiratory rate of tumoral tissues (Di Chiro et al., 1987). It has been demonstrated that amino acid synthesis is up regulated in tumor cells in comparison to normal tissues. Until now, F-Tyrosine and C-Methionine uptakes are studied at different grades of oncologic tumors such as meningimoma (Cremerius et al., 1997).

C-colin, another marker which represents phospholipid synthesis, is hiked in malignant tumors. It has been shown that the metabolism and proliferation of C-colin are strongly correlated with breast and prostate cancers, indicating high uptake as a measurement of cellular proliferation (Cornelius et al., 2011). Other markers, with a better theoretical profile, have also been introduced in neuroscience but are mostly used only in a limited number of experiments, so that no knowledge is about their potential for imaging stem cell transplantation.

4. Near-InfRared Fluorescence (NIRF) imaging

NIRF confers similar capability for tracing of imaging agents as PET. NIRF dyes are chemically conjugated on targeting molecule such as antibodies, carbohydrates and peptides. After administration into tissues, the dye molecules are excited by the radiation of tissue penetrating NIR excitation light (750-900nm).

Considering radioactive decay, a photon of lower energy which has a higher wavelength is emitted and the fluorescent dye relaxes back to its basic state, ready to repeat the same process. Each fluorescent dye absorb excitation light and afterward, just in a nanosecond, produce fluorescent light. Accordingly, each fluorescent dye molecule provides about 100,000,000 photons per second for collection and image formation. As a consequence, low-energy fluorescent photons are slightly absorbed and maximally scattered, reduced by the tissues between the targeted tissue and the tissue surface before being collected by detectors in a few milliseconds. In contrast with radionuclides, a fluorescent dye has no physical half-life. Moreover, this methodology is not clinically approved yet and no devices is available for human imaging with NIRF contrast agents, and NIRF contrast imaging agents do not posses approval for human study as well. Interestingly, some investigators utilized NIRF imaging for human applications such as functional lymphatic imaging, sentinel lymph node mapping, activated probes, and promising advances in 3D imaging (Sevick-Muraca EM, 2012).

5. Potential clinical applications of molecular imaging

Many surgical techniques are mainly based on histological grading of the tumor. Molecular imaging enables surgeons to have the gross picture of these tumors. Pre-surgical molecular

imaging of neurological tumors enables us to establish better surgical procedure and strategy. Also, it would allow physicians to have a better pre-assessment of prognosis and risk benefit ratio. Moreover, PET might be helpful in the early discovery of molecular-level changes, which are undetectable in CT and MRI. Also, within a specific tumor, the most metabolically active and aggressive tumor areas could be mapped.

Intriguingly, emerging data suggest that molecular imaging could be used as an outcome assessment tool for different treatment modalities. For instance, a recent study compared MRI response assessment with metabolic O-(2-(18)F-fluoroethyl)-L-tyrosine ((18)F-FET) PET response assessment during antiangiogenic treatment in patients with recurrent high-grade glioma (see table 1). Good results are already known for (18)FDG-PET, but results revealed that (18)F-FET PET, on the other hand, seems also to be predictive of treatment failure in that it contributes important information to response assessment based only on MRI and response assessment in neurooncology (RANO) criteria (Hutterer et al., 2011).

Gold Standard	FDG-PET diagnosis		FDG-PET diagnosis in brain metastasis patients only		FDG-PET diagnosis in primary tumor patients only		Magnetic resonance imaging diagnosis	
	Tumor (%)	Necrosis (%)	Tumor (%)	Necrosis (%)	Tumor (%)	Necrosis (%)	Tumor (%)	Necrosis (%)
Tumor	47	16	42	17	75	13		
Necrosis	7	3	8	33	0	13	36	9
Sensitivity	75	0	71	0	86	0	94	0
Specificity	81	0	80	0	100	0	50	0

Legend: FDG: ^{6}F-fluoro-2-deoxy-D-glucose; PET: positron emission tomography.

Table 1. (18)F-FDG Positron Emission Tomography with a Gold Standard of Biopsy or Radiography Follow-up (Schaller et al., 2008)

6. Stem cell imaging at neurodegenerative pathways and pathologies

Regenerative medicine is a developing era that seeks to restore or replace damaged tissue and organs via natural or bioengineered tools. Regenerative medicine via stem cells is considered as one of the most promising means to repair tissues. Stem cells could be isolated from both adult human and embryonic tissues. There is a great body of evidence demonstrating successful cases of expanded stem cell in vitro and then grafted in vivo for regenerative purposes at different tissues such as bone, cartilage, and myocardium.

It seems that inflammation and degeneration are the two main aspects of CNS pathogenesis. It seems that there is an intrinsic connection between these two phenomena because in

several cases inflammation trigger degeneration. Also, endogenous neural stem cells, which have the capacity of renewing cells of CNS, may migrate to the affected area and robust the process of repair. This scenario drives scientists to seek a natural healing framework based on Trans stem cell therapy. In fact, it may improve the efficacy and decrease the toxicity of treatment modalities which are the main concepts of personalized medicine.

7. Molecular imaging in Alzheimer's disease

Alzheimer's disease (AD) is describes as a chronic and complex progressive neurodegenerative disorder, and is the most common cause of dementia among the elderly. A great body of evidences indicates that neuronal degeneration in AD progresses in a certain way while the pathology advances over several decades. Establishing an accurate dynamic map of this sequence is vital for the understanding and mapping the complex endophenotype of AD, providing a basis for successful treatments designed to resist or prevent disease progression.

PET scanning has long been used to trace alterations in cerebral blood flow and metabolism in AD, and is useful for the differential diagnosis of dementia in individual patients. For instance, hypometabolism of the posterior cingulate cortex could be observed early in AD using fluoro-deoxyglucose (FDG) PET scanning, even while MRI results are normal (Ewers et al., 2011, Mosconi et al., 2004). As disease progresses, there is diminished cerebral metabolism and perfusion in posterior cingulate and association cortices, but the basal ganglia and thalamus, cerebellum, and primary sensorimotor cortices are largely spared until later stages of the disease. Some studies have tracked AD with PET, using new molecular probes sensitive to amyloid-beta (Aβ) or neurofibrillary tangle pathology, or both types of pathology (Braskie et al., 2010, Klunk et al., 2004, Mintun et al., 2006, Small et al., 2006).

8. Stem cell in Multiple Sclerosis (MS)

Multiple sclerosis appears to result from defective innate and adaptive immune system actions in the CNS, likely begins with a kind of autoimmune response that leads to demyelination and neuronal degeneration. It seems that auto activity of immune system followed by neuroinflamation gradually causes death of oligodendrocytes. Increasing body of evidence represents that the brain's inability to repair is one of the main factors that make this disease irreversible and causes permanent damages. This claim is in accordance with the fact that the progression of disease and state of remyelination is different in every patient. Consistently, Patrikios et al. (Patrikios et al.), recently performed 51 autopsies of MS patients with different clinical courses and disease durations and traced variable extents of remyelination. In 20% of patients – both relapsing and progressive patients – the extent of remyelination was extensive with 60–96% of the global lesion area remyelinated.

Several attempts have been made since about four decades to replace demieylinated cells with myelin forming cells; however, as neural cells are highly differentiated and have limited ability for growth and expansion, these efforts have been mostly abortive in vivo. With the advent of stem cell regenerative medicine, scientists further discovered the

functional and special characteristics of adult stem cells and attempted to utilize them for the treatment of neurodegenerative multiple sclerosis.

Adult stem cells have not only provided us with a readily available cell source for cell therapy but also with much safer and far less toxic tumor treatment measures. There are two basic routes for cell administration including in-site cell transplantation or blood injection (circulation). Tangible examples for the former include Parkinson's disease, acute spinal cord injury and brain trauma. For multifocal diseases such as MS and epilepsy, the model of in-site injection is not effective; rather blood circulation or cerebrospinal fluid circulation should be used. There are several studies demonstrating successful results with the transplantation of hematopietic, mesenchymal and neural stem cells into the CNS injured areas in MS, SCI, epilepsy, and stroke cases (Pluchino et al., 2009).

9. Mechanisms of Stem Cell Repairing

A great amount of data demonstrates that HSCs have a great capacity to differentiate into different cell types including muscle, skin, neural tissue and lung (Pluchino et al., 2009). Several studies used HSCs injection as a treatment modality for hematological malignancies and shows that HSCs have the capability of entering the brain and as well as differentiating and producing new neural cells including neurons and microglia; these findings were in concordance by the detection of Y chromosome- positive Purkinje cells in the cerebellum of female rats who have undergone bone marrow transplantation from male donors (Koshizuka et al., 2004 2005). In addition, in an animal studies on rats suffering from a demyelinated lesion of the spinal cord, intravenous or intraparenchimal HSCs therapy lead to different degrees of remyelination which was proportional to the number of injected stem cells (Akiyama et al., 2002a 2002, Inoue et al, 2003, Akiyama et al., 2002b 2002, Inoue et al, 2003).

Several studies have challenged the idea of cell replacement in stem cell regeneration theories. Despite the fact that MSCs can exert various therapeutic effects, some data suggest that they protect immune system from demyelination via alternative mechanism to cell replacement.

The suggested therapeutic effect is based on the intrinsic capacities of such cells to secret a large number of cytokines and chemokines. It has been shown that the pattern of secretion changes as early as transplanted stem cell encounter new (micro) environment in vivo. Some studies have shown that mesenchymal stem cells mainly act by suppressing inflammation, via cell-to-cell contact as well as through the activation of anti-inflammatory pathways; and consequently the proliferation, migration and differentiation of endogenous progenitor cells are enhanced.

Utilizing fluorescent dyes and imaging modalities in humans is not possible due to limited depth of tissue penetration. On the other hand, magnetic resonance imaging (MRI) and positron emission tomography (PET) have shown promising value and also great feasibility for treatment via stem cell. As well as above PET scan imaging, stem cells could be tagged with ferromagnetic material or with gadolinium rhodamine dextran and then detect via MRI (Brekke et al., 2007) (Carney and Shah, 2011). These imaging modalities along with alteration of genes via genetic engineering and consequent labeling methods, enabled

scientists to monitor different phase of repair and stem cell therapy. This allows not only the imaging in real time of stem cell migration, but also its integration, and therapeutic effects at the single cell level. Also, the above-mentioned capacities for tracing and monitoring of grafted stem cell behavior, enable us to assess both quantitatively and qualitatively the interaction between stem cell and its environment.

10. View to the future

Molecular imaging will gain more and more importance in neurosciences. PET is currently the gold standard and that will not change very soon. However, the different methods have different advantages and disadvantages, but it is not only for the researcher but also for the physician important to know this differences. In the near future, imaging on the molecular but also on the cellular level will not be an exception, as it is still now, but rather the rule. Such improvements open widely the door to a personalized medicine, a fact that has special importance in neurosciences.

11. Take-home-message

Molecular imaging has gained step-by-step importance in neuroscience. To know this method in detail is demanding but important in the area of personalized medicine.

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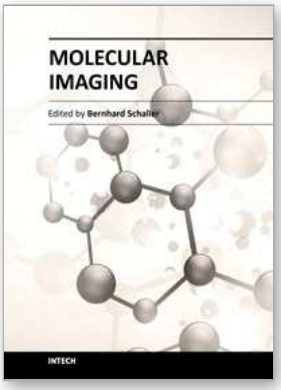

Molecular Imaging

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The present book gives an exceptional overview of molecular imaging. Practical approach represents the red thread through the whole book, covering at the same time detailed background information that goes very deep into molecular as well as cellular level. Ideas how molecular imaging will develop in the near future present a special delicacy. This should be of special interest as the contributors are members of leading research groups from all over the world.

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InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821