Commentary

Molecular Medicine Successes in Neuroscience

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INTRODUCTION

In this issue of *Molecular Medicine*, Irvine *et al.* (1) expound upon the application of molecular biology in clinical medicine and the enabling of targeted interactions at a molecular level over the past decade. In neuroscience, this entails specific interactions with neurons and glial cells. Examples of current research include technologies designed to allow better interaction with neural cells, advanced molecular imaging, materials and hybrid molecules used in neural regeneration, pharmacological neuroprotection, and targeted delivery of drugs and small molecules across the blood–brain barrier. Currently, the most popular molecular medicine topic in neuroscience is the use of molecular imaging techniques. Research on cellular changes has shed invaluable new light on the pathophysiology and biochemistry of neurological diseases. Clinical and experimental use of molecular imaging methods is expanding and now allows quantitative assessment. Molecular imaging may therefore be the best example for the increasing importance of molecular medicine in neuroscience.

Molecular imaging is generally defined as the *in vivo* characterization and measurement of biological processes at the cellular and molecular level (2). In contrast to visualizing the terminal effects of disease, molecular imaging probes the molecular alterations underlying disease, providing additional biochemical or molecular information compared with histological methods and classic neuroradiological diagnostic studies (3). Early identification of treatment success or failure in neurological diseases by molecular imaging could significantly influence patient management by providing more objective decision criteria for evaluation of specific therapeutic strategies. In particular, molecular imaging represents a fresh technology for visualizing metabolism and signal transduction to gene expression. Reporter gene assays, used to trace the location and temporal level of therapeutic and endogenous gene expression, such as in brain tumors (2), open a window to future treatment modalities. Molecular imaging drugs and probes, such as positron-emission tomography (PET), are being developed to image the function of targets without disturbing them, and are developed in mass amounts to modify the target's function as a pharmacological substance (4). Molecular imaging narrows the gap between *in vitro* and *in vivo* integrative disease biology.

Medical and biological imaging has undergone a revolution in the past decade. PET, developed to visualize biochemical and physiological phenomena in living humans and animals (2,3), is the foundation of molecular imaging. Magnetic resonance imaging (MRI), an alternative molecular imaging method, is becoming more influential in neuroscience and clinical neurology (5). Molecular medicine in neuroscience and neurology has several purposes: differential diagnosis, especially in the early stage of neurological disorders; description of pathophysiological changes responsible for manifestation and disease course; and evaluation and follow-up of treatment effects. Many of these applications are possible with the most widely available PET tracer, 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG). Additional tracers are gaining popularity clinically for the detection of specific neurotransmitter and receptor system disturbances, blood flow, oxygen metabolism, or amino acid uptake (4). This functional and molecular imaging technique has progressed rapidly from laboratory research technique to routine clinical imaging modality. Advances in detector technology have led to considerable improvements in the spatial resolution of PET (1–2 mm), enabling investigation for the first time in small experimental animals such as mice (3). Developments in radiochemistry and tracer technology have allowed a variety of endogenously-expressed and exogenously-introduced genes to be analyzed using PET (6). This new knowledge opens up the exciting and rapidly evolving field of molecular imaging, aiming to noninvasively localize biological processes of interest in normal and diseased cells in humans and animal models *in vivo*. In addition to the successful use of PET in basic research, PET is also superior to conventional diagnostic methods in several clinical indications. This is illustrated by detection of biological or anatomic changes which cannot be detected by computed tomography (CT)

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or MRI, especially at an asymptomatic disease stage (6).

The central strength of molecular imaging is the ability to complete the kinetic analysis of a given molecular event in the same experimental subject over time (2,3). This allows noninvasive characterization and phenotyping in animal models of human disease at various disease stages, under certain pathophysiological stimuli, as well as after therapeutic intervention. The potential broad applications of imaging molecular events *in vivo* lie in the study of cell biology, biochemistry, gene/protein function and regulation, signal transduction, transcriptional regulation, and characterization of transgenic animals. Molecular imaging has, for this reason, monumental implications for the identification of potential molecular therapeutic targets, the development of new treatment strategies, and their successful implementation into clinical application.

The incidence of neurodegenerative disorders such as Alzheimer's and Parkinson's diseases, amyotrophic lateral sclerosis, and stroke is swiftly increasing due to an aging population (7) and is expected to have a substantial impact on the future of neuroscience. The field of molecular medicine is rapidly expanding. Advances in the diagnosis and treatment of neurodegenerative pathologies, by atypical molecular materials with the potential to improve diagnosis and therapy, hold promise for the future. Novel technologies to enable these materials to cross the blood–brain barrier will allow efficient systemic delivery of therapeutic and diagnostic agents to the brain. The powerful combination of such molecular materials with cell-based delivery strategies may allow outcomes of neurodegenerative, and perhaps other neurological disorders, to be greatly improved (7).

In this commentary, we detail two molecular medicine applications in neuroscience which are of paramount importance to molecular medicine. These examples illustrate how fundamental pathophysiological knowledge has been transferred to everyday clinical decision-making.

BRAIN TUMORS

Brain tumor cells, especially of higher histological grades, typically have increased metabolic and mitotic rates compared with normal brain tissue (8,9). Malignant gliomas and metastatic tumors are the most common brain tumors. Neuroimaging plays a significant role clinically and experimentally in this disease. In low-grade tumors, neuroimaging is needed to evaluate recurrent disease and to monitor anaplastic transformation into high-grade tumors. In high-grade and metastatic tumors, the imaging challenge is to distinguish between recurrent tumor and treatment-induced changes such as radiation necrosis. The current clinical gold standard, MRI, provides superior structural detail but poor specificity in identifying viable tumors in brain tissue treated with surgery, radiation, or chemotherapy.

^{18}FDG PET has a wide range of possible clinical imaging applications in neurology and neurosurgery, and can provide important prognostic information in primary brain tumors (2). Common clinical indications for PET include tumor delineation and identification of the most metabolically active tumor regions (target for biopsy, differentiation of viable tumor from necrosis) with higher histological grades (III and IV) and shorter postoperative survival period (2,10). For this reason it is helpful to detect transformation of low-grade glioma into a high-grade variety (2,10). Information obtained by molecular imaging influences the choice of subsequent surgical or radiochemotherapeutic options. In addition, response to chemotherapy and radiotherapy is associated with a significant reduction in tumor glucose metabolism (2,10). Further, the spatial relation between brain activated by speech, for example, and the tumor bulk can be explored by activation studies. Therefore, ^{18}FDG PET may provide objective subclinical evidence of response to treatment. The European Organization for Research and Treatment of Cancer PET Study Group recommends a reduction of 15% to 25% in glucose uptake after one cycle of chemotherapy be classified as "partial metabolic response"; and a "complete metabolic response" achieved if there is complete resolution of glucose uptake within the brain tumor volume, such that the brain tumor is indistinguishable from surrounding normal tissue (11). In AIDS patients, ^{18}FDG PET scan may also help distinguish lymphoma from cerebral infections (toxoplasmosis and tuberculoma), since tumoral tissue has a higher glucose metabolism than the infectious lesions (12). The sensitivity and specificity of ^{18}FDG PET in evaluating recurrent tumor and treatment-induced changes can be improved significantly by coregistration with MRI and potentially by delayed imaging 3–8 h after injection.

Other tracers, such as ^{11}C-methionine, also avidly accumulate in brain tumors and have the advantage of low background cortical activity. Similarly, increased uptake of ^{11}C-methionine, which reflects cellular amino acid uptake, is indicative of high-grade glioma and poorer survival (2,10). ^{11}C-methionine is useful for discriminating between recurrences of local or metastatic brain tumors and radiation-induced changes. Recently, ^{11}C-methionine PET demonstrated a sensitivity of 78% and specificity of 100% for differentiating recurrence of metastatic brain tumors from postradiotherapy changes (2,10). However, ^{11}C-methionine uptake may also be elevated in other conditions where there is a disruption of the blood–brain barrier, such as cerebral hematoma, or necrotic areas caused by radiation therapy (2,10). In addition, interindividual ^{11}C-methionine uptake variability does not allow noninvasive grading on an individual patient basis (7).

As a matter of fact, glucose metabolism may be normal or low in lower-grade tumors compared with surrounding cortex. Therefore the combined use of ^{11}C-methionine and ^{18}FDG PET further enhances the accuracy of discrimination

between recurrent tumor and postradiotherapy changes (2,10).

STROKE AND NEURONAL PLASTICITY

Knowledge acquired from PET cerebral blood flow and metabolism studies has significantly contributed to the development of thrombolysis as a treatment modality in ischemic stroke (4,13). Based on evidence from PET, multimodal imaging is increasingly recommended and reveals the presence of considerable pathophysiological heterogeneity from patient to patient, which is largely unpredictable from the time of onset or clinical deficit. While these observations are the underpinnings in key trials of thrombolysis, they also indicate that only patients who are likely to benefit should be exposed to its risks. Accordingly, imaging-based diagnosis is rapidly becoming an essential component of stroke assessment, replacing the clock with individually customized management. After stroke, molecular imaging by PET can identify a core region of irreversibly damaged tissue with profoundly depressed cerebral blood flow and metabolism. This core region is surrounded by the penumbra, an area of hypoperfused tissue with relatively normal oxygen consumption, which may be salvaged by reperfusion (4,13,14). Survival of the penumbra correlates with degree of recovery after ischemic stroke (15). The possibility of finding a penumbra and its extent decreases as time from stroke onset increases. One study showed that 90% of patients studied within 6 h of stroke onset still exhibited a substantial amount of cortical penumbra. Such findings are detected in about a third of patients even at 5–18 h after onset (13). Beyond thrombolysis, knowledge of the individual pathophysiology also guides management of variables such as blood pressure, blood glucose, and oxygen saturation, which can otherwise precipitate the penumbra into the core, and the oligemic tissue into the penumbra.

Results from several PET studies suggest that recruitment of remote areas and functional reorganization are possible mechanisms for the recovery of cerebral functions in adult brains after stroke. One $H_2{}^{15}O$ activation study revealed patients who recovered from hemiplegic stroke showed bilateral activation of motor cortices during finger movement of the affected hand, whereas movement of the normal hand's fingers only resulted in the activation of the contralateral motor cortex and the ipsilateral cerebellum (16). In another study, patients with nonfluent aphasia due to left anterior perisylvian infarction, including the left pars opercularis with subsequent recovery, were compared with two control groups: normal subjects and anterior aphasic patients with sparing of the left pars opercularis (17). During production of propositional speech, the left pars opercularis infarct group showed increased activation of the homotopic right pars opercularis when compared with the two control groups. Further understanding of the mechanisms underlying neuroplasticity will help clinicians, scientists and researchers design appropriate strategies for rehabilitation and identify patients who are most likely to benefit from such therapy.

Similar neuroplasticity is seen in neurodegenerative conditions, a topic underscored by Irvine *et al.* (1). The term neuroplasticity encompasses all possible mechanisms of neuronal reorganization including: recruitment of pathways that are functionally homologous to, but anatomically distinct from, damaged pathways (*e.g.* nonpyramidal corticospinal pathways), synaptogenesis, dendritic arborization, and reinforcement of existing but functionally silent synaptic connections (particularly at the periphery of the core lesion). The study of neuroplasticity has clearly shown the ability of the developing brain—and of the adult and aging brain—to be shaped by environmental inputs both under normal conditions (that is, learning) and after a lesion. In Parkinson's disease, there is a decrease of contralateral putaminal. ^{18}F-dopa K_i by about 50% before symptoms develop (18). Whone *et al.* (19) showed a lack of significant clinical progression despite continuing loss of nigrostriatal projections in early Parkinson's. This is likely due to the upregulation of nigropallidal dopaminergic projection to globus pallidus internus (GPi), and is evidenced by increased GPi ^{18}F-dopa K_i, compared with healthy volunteers, reducing inhibitory output from GPi to the thalamus. Such compensatory changes are not seen in more advanced Parkinson's with motor complications. These results may partially explain why patients with early Parkinson's disease often respond well to dopaminergic medications with few clinical fluctuations. Loss of nigropallidal upregulation may result in alteration of the firing pattern of GPi from tonic to burst firing, heralding the onset of motor complications.

In conclusion, molecular imaging by PET is a new and important, though expensive, neuroimaging tool. Although the exact role of molecular imaging in these disorders has yet to be defined, molecular imaging is an exceptional example of molecular medicine's impact in daily neuroscience. Successful codevelopment of neuroimaging surrogate markers and preventive treatments might eventually lead to brain-check scans for determining risk of cognitive decline. Physicians may then administer disease-modifying medications, vaccines, or other interventions to avoid future cognitive losses and delay disease onset. PET should be judiciously used due to its high costs and poor accessibility. Undoubtedly, the story of success of molecular imaging in neuroscience will continue rapidly.

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