Potential Impact of Molecular Imaging in Oncology

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Abstract. Despite all progress in molecular imaging methods, the actual number of validated new markers is still limited. The breakthrough of individual efforts is often hampered by lack of critical mass of resources. To overcome these shortcomings a "network" of multidisciplinary experts is indispensable. Focusing on cancer therapy, molecular imaging has a high potential impact in (a) early therapy monitoring and (b) prediction of therapeutic response. Novel molecular markers with high diagnostic potential reflecting apoptosis, proliferation and glucose metabolism are currently used in clinical trials for monitoring of tumor response to therapy. A further innovative approach for supporting individualized cancer therapy may be the application of radio-labelled therapeutic drugs at tracer concentrations in order to estimate their individual uptake in the tumor tissue. To meet this challenge, our group initiated a research project focusing on radio-labelling of selected molecules with proven therapeutic potential.

Molecular-based imaging technologies have gained wide acceptance for detecting, localizing and monitoring tumor tissue and have been included into clinical patient care. The spectrum of available probes extends from radiiodine for imaging of differentiated thyroid cancer up to radioactive-labelled deoxyglucose as a marker for the increased metabolic activity of tumor tissue.

However, in the state-of-the-art oncology practice, there is a growing demand for individually optimized treatment strategies. In this context, there are two major challenges addressed to molecular imaging. Imaging specialists are asked for markers suitable to (a) assess tumor response early after initiated treatment in order to allow transition to a second-line therapy, and more recently, (b) to provide methods to predict tumor response prior to an intended therapeutic regime.

The scientific background to meet these challenges is our increasing knowledge about molecular mechanisms of human (patho-) physiology and diseases. The latest results of genomics and proteomics have contributed to our further understanding of present imaging methods and stimulated the development of innovative molecular imaging probes and technologies.

An example of the consequences from the advances in molecular biology is the pivotal role of the Sodium-Iodine-Symporter (NIS) and its diagnostic and therapeutic implications in thyroid and non-thyroid cancer. Cloning the NIS gene in 1996 opened the door to the evaluation of new therapeutic options by transfer of the NIS gene in non-thyroid tumor cells. Here, the NIS gene delivery was shown to be capable of inducing an accumulation of both diagnostic and therapeutic amounts of radioiodine even in non-thyroid tumors.

The introduction of new agents for target-specific radiotherapy was pioneered by the use of the radio-labelled antibody Rituximab (Zevalin™). Zevalin™ is now approved as a new treatment modality for patients with refractory B-cell non-Hodgkin’s lymphoma. The therapeutic regime considers two labelling approaches: the application of gamma-emitting radio-labelled compounds in a first step serves as a therapy predictor, the beta-radiation emitting variant acts – in a second step – as a therapeutic agent.

This "predictive strategy" in cancer treatment, the challenge of the systematic use of small amounts of radio-labelled therapeutic drugs for quantitative measurements prior to a foreseen therapy, is still limited to the two examples described above. Since regional tumor uptake of radio-labelled variants of therapeutic molecules presumably correlates with therapeutic response, a molecular imaging approach might be an efficient tool for the prediction of the therapeutic effect. However, implementation of such an individualized treatment in clinical oncology needs completely new structures of tracer development.

Our group is working on the definition of an international scientific network for elaborating technological pipelines for
radio-labelling of innovative drugs, i.e. new chemo-
therapeutics, plant lectins etc. and monitoring the time course
of their in vivo distribution in animal models of cancer (1).
At a later stage, the evaluation of these new markers in
clinical trials in co-operation with the industry is foreseen.

Another important aspect of molecular imaging of cancer
is the introduction and validation of new markers for therapy
monitoring (2, 3). Research efforts in this scientific field are
stimulated by the enormous cost of state-of-the-art
chemotherapy as well as by the severe side-effects of often
inefficient therapy (4).

As an increased glycolysis rate is a property of tumor
cells, 18F-deoxyglucose (18F-FDG) is widely used to
visualize accelerated glucose transport into the tumor cells.
The first clinical trials for therapy monitoring by 18F-FDG
basically revealed the suitability of this marker for the
prediction of therapeutic outcome (5). In order to separate
specific molecular signals of metabolic tumor activity from
therapy-induced inflammatory reactions, a long time
interval between the prior treatment and imaging is
mandatory. Thus, optimal timing of 18F-FDG seems crucial
since a transient increase in stromal reaction may result in
an overestimation of the fraction of viable cells.

Recent insights into the basic mechanisms involved in
tumor response indicate that membrane changes associated
with apoptosis are a key early step of programmed cell
death and, therefore, a "specific state" of early tumor
response to chemotherapy. Annexin V binds to
phosphatidylserine (PS), a component normally found on
the inner layer of the cell membrane, whose appearance on
the outside of the plasma membrane is a hallmark of
apoptosis (programmed cell death). Annexin V has a high
affinity for cell or platelet membranes with exposed PS in vitro and in vivo. This observation led to both testing of
radio-labelled Annexin V in vitro in a T-cell lymphoblast cell
line and in vivo in animal models of apoptosis. These studies
showed that the uptake of radio-labelled Annexin V
specifically identified apoptotic cells. Due to its biological
property, Annexin V has been investigated for non-invasive
evaluation of early response of tumors to anti-cancer
therapy within 20 hours or less of treatment initiation.

A further possible molecular target of therapy
monitoring is the activity of the cellular thymidine kinase-I,
which is strongly connected to the rate of cellular
proliferation (6). The corresponding probe, the 18F-labelled
deoxythymidine (18F-FLT), is currently under evaluation in
several clinical trials.

In conclusion, molecular imaging offers promising new
ways for the diagnosis and therapy of cancer reflecting
clinical needs for individualized therapy planning and early
therapy monitoring. However, an effective and durable
structure of a "critical mass" of researchers, resources and
industrial structures will be indispensable for the
development of clinically helpful molecular markers.

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