Biology and Pathology

Cancer Biology

Biomarkers – Oncology and Inflammation
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Learning Objectives:

- Understanding the concept of biomarkers
- Hallmarks of Cancer

In a seminal paper, Hanahan and Weinberg [1] defined characteristics of cancerous tissue. Those included insensitivity to antigrowth signal, self-sufficiency in growth signals, limitless replication potential, evasion of apoptosis, angiogenesis and infiltration and metastasis formation. This list was later extended to include deregulation of cellular energetics, avoidance of immune destruction, genomic instability and tumor promoting inflammation [2]. Many of these phenotypic hallmarks can be assessed using imaging, which is attractive both with regard to improved diagnosis as well as for therapy management complementing the established structural readouts based on computer tomography (CT) and magnetic resonance imaging (MRI). While clinical diagnosis is commonly based on qualitative interpretation of imaging data, assessment of therapy response relies on quantitative readouts. In oncology response criteria for solid tumors (RECIST) have been established and recently revised [3]. Yet, structural readouts are in general late indicators of response. In contrast, it has been shown that physiological and metabolic tissue parameters are highly susceptible indicators of the tissue state and can be used as biomarkers of prognostic quality. Such biomarkers are of course of high interest for therapy evaluation and management. Three potential readouts which are currently being used in this context are positron emission tomography in combination with 2-[18F]-fluoro-2-deoxyglucose (FOG-PET) to assess glucose utilization, dynamic contrast enhanced MRI (DCE-MRI) to assess vascular leakage as measure of angiogenesis, or PET using [18F]-fluoro-thymidine to assess proliferation.

Commonly, such biomarkers do not substitute for a clinical endpoint, which might be tumor shrinkage or patient survival, but rather provide early information that the patient is responding to treatment. They are typically used in proof-of-concept studies, clinical studies with a small group of patients demonstrating the validity of the pharmacological strategy/mechanism. For example, it has been shown with FOG-PET studies that treatment of patients suffering from gastrointestinal stromal tumors with a tyrosine kinase inhibitor [4] or of melanoma with B-rat inhibitor [5] led to significant reduction of tumor glucose utilization within days after treatment onset. Similarly, it has been shown that anti-angiogenic drugs reduce tumor vascular permeability with a few days of treatment [6].

Critical aspects in biomarker studies are aspects such as robustness, accuracy, and reproducibility, implying a careful validation of the imaging approach. Given the heterogeneity of the patient population the typical study de sign consists of pre- and post-treatment measurements in the same individual. Recording two baseline data sets is strongly recommended. Also, proof-of-concept studies may be conducted at different sites which demands for stringent standardization of data acquisition and analysis procedures as well as rigorous quality assurance/quality control in order to deliver comparable

results. Guidelines worked out by consortia of stakeholders should warrant this (for DCE-MRI see [6]). Of course these guidelines are under constant revision as novel opportunities emerge, e.g. the implementation of analysis methods that explicitly account for tumor heterogeneity.

The availability of validated biomarkers providing early information on potential outcome will be of tremendous value for patient management and will become an indispensable tool for the treating physician and for the therapy developer.

References:

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