The role of molecular and imaging biomarkers in the evaluation of inflammation in oncology

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With the progress of the new targeted and costly anticancer therapies, the need for novel and early diagnostic and prognostic strategies to identify patients who are likely to benefit from them is increasingly evident.

The mounting interest in personalized (or precision) medicine has to be interpreted in this context in which individually tailored therapeutic approaches are the ultimate goal of an increasing number of clinical trials. The development of personalized medicine has been driven by the amazing advances in technologies that have occurred over the last two decades, which have led to both a substantial increase in knowledge of cancer biology and the availability of biomarkers related to cell machinery mechanisms. In the meantime, the definition of “biomarker” has been revised and broadened to “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.” As a “characteristic” the set of biomarkers encompasses molecular characteristics, imaging information, and clinical and demographic aspects, thus facilitating the integration of an increasing amount and variety of information in the toolkit to tailor to individual patient’s characteristics. In this perspective, A_IATRIS organized an educational initiative aimed at facilitating the collaboration among academics, physicians, and developers, focused at bridging knowledge and skills from two interacting platforms (Biomarkers and Imaging & tracers) on the crucial area of biomarker research concerning inflammation and cancer.

Inflammation is considered one of the factors that promotes cancer development. Epidemiological evidence has assessed that chronic inflammatory disease increases the risk for developing several types of cancers, promotes tumor progression, and enables its metastatic capacity.

Deeper understanding of the functional interactions of immune cells within the tumor microenvironment have allowed the identification of new biomarkers and the development of more successful and non-toxic anticancer-targeted treatment. For these reasons, the impact that biomarkers in cancer inflammation could have in cancer screening, diagnosis, and treatment is crucial.

Due to developments in technology, a number of tissues and fluids can be analyzed for identifying and quantifying cancer biomarkers. Advances that have allowed discovery, identification, and characterization of a large number of analytes in biological complex matrices have revolutionized biomarker discovery. Despite the progress made, very...
few biomarkers have been translated into actual clinical practice, and many of these biomarkers have not even been found reliable.\textsuperscript{5,6}

There is a gap between biomarker research and clinical utilities. This gap could be partially filled by critical discussion on the appropriate choice of tumor markers and the appropriate guidelines based on evidence of their clinical benefits.

Circulating biomarkers are gaining interest in cancer research due to the many advantages with respect to tumor tissue biomarkers, but their clinical role is, at present, rather restricted. Several studies reported that constituents of tumors, which are extruded into the blood stream and into other body fluids, can be identified in liquid biopsies: circulating tumor DNA tumor-derived cells, circulating tumor cells, or circulating microRNA. These circulating biomarkers could be used to reveal cancer at early stages, to monitor tumor progression, and to detect tumor relapse in a minimally invasive approach.\textsuperscript{7,8} Another critical aspect is the heterogeneity between and within cancer patients to drug response. To overcome these obstacles, predictive biomarkers have been recently developed to guide oncologists in the selection of cancer patients who will respond to various antitumoral treatments.

The accumulation of big data deriving from multi-OMICS approaches—ranging from genomics to metabolomics—provides a unique chance for the systems biology science to reveal the complexity of cancer cells through the standardization of experimental data and computational models. In future, a systems-biology-based approach could better predict the phenotypic changes of cancer cells and their interaction with the microenvironment upon anticancer treatment.\textsuperscript{9,10}

On the other hand, therapeutic strategies such as immune-based therapies also evoke an inflammatory modulation, with the consequence that it can be difficult to distinguish an increase of tumoral mass or metabolism as a result of pseudo-progression from true disease progression. The importance of distinguishing between inflammation or cancer progression early and exploiting this complex network of inflammatory cells and signals, which offers new targets for cancer diagnosis and treatment, is evident in this scenario.

Medical imaging is widely used for non-invasive assessment of tumor response or progression. Several emerging imaging modalities, including metabolic imaging (positron emission tomography (PET), single-photon emission computed tomography (SPECT), magnetic resonance spectroscopy), functional magnetic resonance imaging (fMRI), radiomics (computed tomography, MRI), and molecular imaging (PET, SPECT), can provide important features that describe tumor biological behavior and the peritumoral microenvironment.\textsuperscript{11-13} The use of imaging-based biomarkers has shown great potential to predict clinical responses to therapies in a wide spectrum of tumor types.

Tumor microenvironments contain many different inflammatory cells and mediators offering several targets for early diagnosis and the development of innovative treatment strategies. The tumor microenvironment can enhance or reduce cancer progression due to the presence of stromal, malignant, immune, and endothelial cells. Depending on their polarization status, several subsets of leukocytes may have a pro- or anti-tumoral function through the secretion of cytokines, chemokines, or growth factors. The complex interaction between the tumor microenvironment and the host immune system, would suggest new biological targets for identification of inflammatory process or tumor monitoring and treatment.

Tumour hypoxia is also present in many cancer types and has prognostic and predictive value to both radio- and chemotherapy.\textsuperscript{14} Hypoxia in cancer has been associated with aggressive tumor phenotypes that are characterized by rapid progression, treatment resistance, and poor prognosis. Intratumour heterogeneity of hypoxic regions also represents a challenge for clinical practice in oncology. Quantification of hypoxia in several cancer types by using functional imaging-based biomarkers allows image-guided treatment adaptation and personalization.

Several studies indicate that decreased extracellular pH induces (independently from hypoxia) hematogenous and lymphatic spread of tumor cells worsening the long-term prognosis of tumor patients.\textsuperscript{15} This extracellular acidosis, resulting from anaerobic or aerobic glycolysis in combination with a reduced removal of acidic metabolites, induces and selects for malignant behaviors, such as increased invasion and metastasis, chemoresistance, and inhibition of immune surveillance.\textsuperscript{16} This metabolic reprogramming, which occurs during adaptation to acidosis, introduces therapeutic vulnerabilities, thus making tumor acidosis an important therapeutic target.

Another emerging field of interest is represented by those studies that integrate imaging parameters with molecular biomarkers for improving patients’ diagnoses and prognoses. A closer integration of imaging with related biomedical fields and the creation of large integrated and shareable databases of clinical data are recommended,\textsuperscript{17} as well as the creation of imaging biobanks to provide large bioimage datasets for radiomics analysis.

An interesting element of support to pathologists can be derived from the development of ex vivo multispectral imaging technology to visualize up to six biomarkers in the same sample.\textsuperscript{18} With this technology, it is possible to identify not only cancer cells, immune cells, stromal cells, and endothelial cells, but also the expression of certain molecules (e.g. the programmed cell death receptor 1), which are specific for tumor-infiltrating lymphocyte in situ and could be predictive of clinical outcome in several cancers.

The choice of these topics (inflammatory microenvironment and cancer) is the result of an integrated effort of two A_IATRIS platforms (Biomarkers and Imaging &
tracers). While in no way pretending to be exhaustive, we believe that to deal with these aspects, merging two different points of view could bring wider vision and new perspectives in personalized cancer treatment.

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