Pathology and Tumor Microenvironment: Past, Present, and Future

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Every case of neoplasia examined microscopically by the pathologist involves analysis, besides the presence and architecture of cancer cells, the features of tumor microenvironment (TME), including blood vasculature, desmoplastic reaction of the stroma, and signs of inflammatory reaction in the tumor surroundings. Histopathological diagnosis and assessment of prognostic as well as predictive factors become possible only after considering all of the above features. Long time ago, pathologists have already recognized particular components of the TME. Pierre Masson [1] in his “Human Tumors” described the stromal reaction and its histological forms as early as in 1957. He set apart late, synchronous, or precocious stromal reactions, depending on the time of their appearance. Among histological forms, he discerned inflammatory, irritative, or vascular types. Cellular characteristics of the first form featured polymorphonuclears, eosinophils, lymphocytes, and plasmacytes, with variable contribution of particular cell type and dominance of histiocytes and lymphocytes. Pierre Masson pointed to the presence of proliferating fibroblasts among inflammatory infiltrating cells. He compared late stages of stromal reaction to a scar. An important aspect of the irritative type morphology was the vasculature forming a tight meshwork around the neoplasm as in the placenta. On the other hand, vessels’

multiplication in the tumor and around it constituted features pointing to the vascular type of stromal reaction.

The advent of novel biomedical research technologies in the seventies of the 20th century brought intensive developments in TME research. Isolation of a tumor factor responsible for angiogenesis by Folkman et al. [2] set focus on cancer-associated angiogenesis. Almost twenty years later, Leung et al. [3] identified vascular endothelial growth factor, which became a target of anti-angiogenic cancer therapy. After subsequent fifteen years a drug based on this discovery was approved for clinical use [4]. Consecutive years saw the advent of vascular endothelial growth factor inhibitors as well as inhibitors of various kinases. In another development, immunohistochemical technologies allowed to explore the nature of tumor-infiltrating lymphocytes (TILs) [5]. It was discovered that lymphocytes B and T, as well as natural killer cells are present among TILs. Their cytotoxicity was investigated [6]. Rosenberg et al. [7] discovered that adoptive transfer of TILs, led to effective antitumor response. Gross et al. [8] designed, in turn, chimeric immunoglobulin T-cell receptors. This was the starting point for developing a novel method of treating hematological malignancies, as well as solid tumors based on chimeric antigen-receptor T cells [9].

Another type of cells scrutinized in the seventies and eighties of the last century in the TME context were macrophages. Studies showed that tissue-associated macrophages could act both as anti-tumorigenic as well as pro-tumorigenic agent [10]. Similar properties were attributed later to dendritic cells [11, 12].

Already in the eighties, fibroblasts associated with tumor stroma (cancer-associated fibroblasts) were characterized as differing from those in normal skin [13]. It turned out that cancer-associated fibroblasts contribute to tumor progression via release of various cytokines [14].

The phenotypic expression as well as proliferation of tumor cells can be modulated by their adhesive interactions with the extracellular matrix; this was described in 1980 by Vlodavski et al. [15]. The ability of the extracellular matrix to undergo remodeling is a feature enabling tumor progression [16]. Desmoplastic stroma in advanced cancer stages can complicate penetration of drugs and facilitate progression [17].

Effectiveness of anti-cancer treatment is affected directly (and indirectly) by the specific composition of cellular constituents, various mediators released as well as physical properties of TME [4].

Currently, one of the most important issues concerns cancer stem cells/cancer-initiating cells, which are subpopulations within tumors and responsible for tumor formation, progression, and resistance to therapies [18].

Dynamic developments in TME studies resulted in organizing The First International Conference on Tumor Microenvironment: Progression, Therapy and Prevention in 1995, next formation of the International Cancer Microenvironment Forum, which upgraded into the International Cancer Microenvironment Society in 2003, as well as appearance, since 2008 Cancer Microenvironment journal [19].

After five decades of intensive and fruitful efforts undertaken by research communities worldwide we have witnessed the results of TME studies to be harnessed to anticancer therapies.

TME topic is an interdisciplinary issue with overlapping biology, pathology, and clinical approaches. The key role of the pathologist in the context of TME issues is to search for and validate novel biomarkers that could be implemented using standardized methods and applied to the clinic [20, 21]. In 2012, an international research group led by Jerome Galon has proposed on the pages of the *Journal of Translational Medicine* to begin incorporating the “Immunoscore” into traditional cancer classification [22]. He assumed that international validation of this factor as a biomarker in routine pathological diagnostics can bear fruits with a novel component of tumor classification TNM-I (TNM-Immune) and facilitate clinical decision-making. This initiative was indeed echoed by pathologists and clinicians and resulted in numerous studies of various tumors [23]. However, according to AJCC 2017, this was not reflected by the latest TNM classification [24]. Among new WHO editions of tumor classification, only breast tumors present TILs as prognostic marker in level 1b evidence [25]. Tumors per se, as well as TME interactions, form extremely complex, multilevel dynamic systems that culminate in very heterogeneous phenotypes. Such phenotypes are routinely encountered by pathologists during their microscopic, immunophenotype, or molecular scrutiny.

Nevertheless, we are squarely faced with the question: in what direction will tumor pathology be heading in the era of rapidly advancing knowledge about TME?

Pathologists and biologists join ranks in presenting a solid state-of-the-art outline of knowledge about morphological pathomechanisms affecting the microenvironment of various neoplasms – both those that have already found clinical use and the ones that soon will find their way into the clinical armamentarium. It is my hope that the reader can find at least a partial answer to this question in papers that make up this special issue.

Disclosure Statement

The author has no conflicts of interest to declare.

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