Preface: Tumor-Stromal Crosstalk In Oncogenesis

This special issue addresses one of the most published and relevant fields of research in cancer. In contrast to a half century ago, virtually any article on pathogenesis, invasion, metastasis, and even therapy currently discusses not only the cancer cell *per se*, but its environment and interaction with stromal cells (fibroblasts, endothelial cells, macrophages and other immune or inflammatory cells, including vasculature, local elaboration of cytokines, and other factors) in a bidirectional highway between tumor and nontumor cells. Particularly fascinating are the genetic changes that each compartment (tumor and stroma) has on the other, thus supporting the old field theory of oncogenesis. In other words, are adjacent cells truly normal? Do the cancer cells induce genetic changes on their neighbors? Or are these alterations already present as part of oncogenesis in any tissue? Are these mechanisms responsible for the heterogeneity within a single cancer deposit, or between primary and secondary neoplasms, as well as between metastases? Such genetic heterogeneity is becoming of increasing interest and concern[1-3] and rightfully so if a biopsy is to be representative for determining any "personalized" therapy. This suggests that cancer is not a uniform or a clonal collection of cancer cells, but is part of a community containing different populations of various states of malignancy, diversity, and genetic makeup. Adjacent cells in the stroma are critical to the progression and fate of the cancer cells, including provision of nutrients, growth, and other soluble factors such as oxygen, epigenetic and genetic signals, and other components of the microenvironment. Further, these may not be identical for the primary neoplasm and its local and distant metastases, as well as between metastases residing in the same or different organs. Given this heterogeneity on several levels, it is astounding that there are certain common or standard therapies for different cancer types, but the results generally support the view that identification of specific and dominant altered genetic pathways may be the most rational approach to therapy. Indeed, the diversity resulting from tumor–stromal crosstalk will remain a challenge for overcoming resistance as well as a challenge for those who wish to enhance the use of interventions that affect both cancer cell populations and their diverse microenvironments. Finally, there is no reason to assume that these interactions will be identical for diverse cancer types, such as liquid vs. solid tumors or among different cancer subtypes.

Given the multiplicity of topics that can be discussed in the topic of this special issue, I have decided to emphasize how cancer cells transmit genetic information to stromal cells, with particular focus on cell–cell fusion, a subject that I have studied sporadically since 1968, when I proposed that in-vivo cell fusion is a biological mechanism for the progression of malignancy.[4-8] Subsequently, we reported that neighboring murine fibroblasts in human tumors grafted in nude mice showed a horizontal transmission of malignancy, forming fibrosarcomas,[9,10] an observation already made at the beginning of the last century by Ehrlich and Apolant, implicating "chemical substances" transmitted from the epithelial tumor cells to form sarcomas in mice.[11] Finally, how tumor–stromal crosstalk can be exploited in therapy interventions also is addressed in several of these articles.

The vast literature on cell–cell fusion, spanning over a century, is reviewed concisely by Parris, yet provides a comprehensive bibliography. His insightful discussion addresses the importance of mutations and aneuploidy, the partnership of bone marrow-derived cells in fusions facilitating metastasis, and the role of viruses in cell–cell fusion. He is clearly the honorary historian of this subject and provides a stimulating perspective.

Harkness, Weaver, Alexander, and Ogle discuss cell fusion from an evolutionary and general biological perspective, including the role of polyploidy and nuclear reprogramming in healing, regeneration, and cancer. They review various mechanisms of cell fusion, and then address its role in oncogenesis, particularly tetraploidy and telomere crisis in genetic diversity and instability. They also cover how these concepts relate to cell fusion and metastasis, including cell fusion between tumor cells and cell fusion with local non-malignant cells, as well as bone marrow derived cells. Finally, these authors present novel methods to detect fusion products.

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Seygried and Huysentruyt review various theories explaining cancer metastasis and present evidence, including their own research, that metastasis is a macrophage metabolic disease, in which macrophages either transform or fuse with cancer cells to become metastatic. They then apply some of their provoking concepts to a nutritional therapy for glioblastoma multiforme.

Cives, Ciavarella, Dammacco & Silvestris report on cell fusion in tumor progression by studying the myeloma marrow microenvironment. This is particularly relevant because of the report of fusion of multiple myeloma cells with osteoclasts by Andersen and collegues.[12] Cives and coauthors summarize clinical and molecular evidence of the role of cell fusion in multiple myeloma, focusing on the contributions of various cells within the multiple myeloma microenvironment in the progression of this neoplasm, particularly the fusogenicity and osteoclastogenic potential of myeloid progenitors and dendritic cells. They also discuss fusogenic proteins in the myeloma marrow milieu, and the functions of osteoclasts resulting from fusion of marrow monocytes/macrophages. These authors emphasize the "neoplastic unit" comprising the interaction between malignant plasma cells, bone marrow stem cells, osteoblasts, and osteoclasts within the marrow microenvironment, proposing that cell fusion may be involved in multiple myeloma pathogenesis and myeloma-related bone loss. These important issues could lead to therapeutic strategies to prevent bone loss and control myeloma progression.

Berndt, Zänker & Dittmar review the development of drug resistance via cell fusion. They postulate that, due to aneuploidy and genetic instability, hybrid cells have an enhanced capacity to withstand cellular stress and gain drug resistance. They further speculate that cell fusion could result in cancer stem cells (CSC), and introduce the concept of recurrence CSC, where tumor recurrences become resistant to first-line therapy. The implication is that blocking of cell fusion within cancers could prevent the development of more malignant cells in terms of enhanced metastatic potential and drug resistance.

Using mammary cancer models in mice, Reisfeld presents a number of innovative experiments by his group involving the combination of immunological and chemotherapy approaches, emphasizing targeting constituents of the tumor microenvironment (TME) such as tumor-associated macrophages (TAMs) and cancer-associated fibroblasts (CAFs). He uses such targets as legumain (asparaginyl endopeptidase), proto-oncogene Fra-1, transcription factor State3, fibroblast activation protein, and HER-2. The development of DNA vaccines against such factors overexpressed on breast cancer cells, as well as TAMs and CAFs, confirms that these TME targets can affect tumor growth and dissemination in such murine models, especially when combined with chemotherapy strategies. Thus, he shows how various immune cytokines and growth factors in the tumor microenvironment can be manipulated to treat such breast cancers, and he interrogates the role of Th1/Th2 macrophages in these processes.

Whatcott, Han, Posner & Von Hoff focus on pancreatic ductal adenocarcinoma (PDAC), a cancer with a strikingly high mortality rate, and point to the unique tumor–stromal interactions of this neoplasm that contribute to its poor prognosis. These authors emphasize integrin and CD44 signaling, the increased deposition of hyaluron (extracellular matrix glycosaminoglycan), and the role of CAFs in the production of many of the stromal components of PDAC, such as, insulin growth factor, epithelial growth factor, and transforming growth factor β (TGFβ); the latter has been correlated with a poor prognosis. They also report their group's studies in a genetically-engineered mouse model of PDAC, where hyaluronidase treatment decreased interstitial pressures and resulted in an improved survival. This provides a potential lead to how tumor–stromal targeting may improve drug penetration and activity.

The final article of this issue returns us to the question of the horizontal transmission of malignancy, but in this case by cell-free nucleic acids circulating in the plasma of cancer patients. Dolores and Damien Garcia-Olmo review this intriguing subject and provide a summary of their novel results showing that DNA from human plasma of colorectal cancer patients can induce tumors in immunodeficient mice after murine NIH-3T3 fibroblasts are transformed *in-vitro* with this human DNA. Moreover,

the murine-induced tumors expressed human K-ras sequences that were positive in the patients' tumors. These authors posit a *Theory of Genometastasis* and review evidence from other lines of experimentation including nucleic acid transfer via exosomes and microvesicles. Hence, other mechanisms besides cell–cell fusion can explain the horizontal transmission of malignancy from tumor to stroma.

Overall, this issue does not pretend to be a comprehensive summary of the many aspects of the tumor microenvironment and how tumor cells interact with various stromal cells in a bidirectional manner. Instead, the major emphasis is an introduction of different and even somewhat controversial views on cancer progression, especially metastasis, involving various genetic and epigenetic mechanisms, as well as innovative theses on cancer therapy involving targeting hybrid cells and stromal targets.

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