Cancer and Metastasis Reviews (2019) 38:331–332
https://doi.org/10.1007/s10555-019-09817-1

Preface to "Proteases in Cancer Progression and Metastasis" special issue

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Published online: 24 October 2019

A key role for proteases in various aspects of cancer progression and/or metastasis has been known for decades. The focus at that time was primarily on the earlier described members of the serine, cysteine, and matrix metalloprotease (MMP) subclasses such as urokinase or urinary plasminogen activator (uPA), cathepsins, and the secreted MMPs. Their reported action was through intra- and extra-cellular signaling mechanisms and/or degradation of components of the extracellular matrix (ECM) of the tumor microenvironment to facilitate tumor growth and invasive processes at both the primary tumor and metastatic sites. However, in recent years, the repertoire of proteases described has grown exponentially as has our knowledge of their action in cancer progression and metastasis. The serine and MMP classes have expanded to include cell-surface anchored or membrane-bound proteases such as the membrane-bound MMPs, meprin metalloproteases and transmembrane type II serine proteases (TMPRSS), and the secreted Kallikrein-related (KLK) serine proteases. Concurrently, with the more sophisticated genome and protein technologies available to us, we now have access to large transcriptomic and proteomic datasets underpinning the proteolytic action of these proteases that not only better describe their precise action in the tumor microenvironment but also indicate a broader involvement than previously thought in cancer progression and metastasis, particularly in signaling mechanisms.

In this special issue, two articles by Peters and Becker-Pauly and Martin and List, respectively, describe the role of two of these recently described new subclasses—meprins and TMPRSS—in the tumor microenvironment and metastasis. The secreted KLK protease, prostate-specific antigen or PSA, is the currently used serum biomarker for prostate cancer diagnosis and treatment monitoring. Moradi et al. look beyond that biomarker role to explore the functional role of PSA in the prostate tumor microenvironment and the potential of PSA-targeted imaging modalities and therapies for prostate cancer. Ji et al. describe live-cell *in vitro* imaging techniques to view the proteolytic action of proteases, such as the cathepsins, in the breast cancer microenvironment using 4D spatio-temporal modeling of breast cancer avatars. Such sophisticated models are critical to advance our understanding of not only the role of proteolysis in ECM degradation, but also the signaling pathways generally perturbated in the tumor microenvironment.

Several articles describe relatively recently described novel processes associated with tumor progression and metastasis and in which proteases are also increasingly being reported to have a role. Mitschke et al. describe the role of several extra- and intra-cellular protease classes (MMPs, ADAMs, TMPRSS, cathepsins, deubiquitinating enzymes) in epithelial-to-mesenchymal cell transition (EMT), a critical process required for tumor cells in both local invasion at the primary tumor site and metastasic spread. Das et al. focus on exosomes as a storehouse of tissue remodeling proteases and mediators of cancer progression. Exosomes have been recently shown to be an important regulatory route for exporting critical regulators of the cellular microenvironment to the cell surface and secretion from the cell. Their review highlights the critical roles of exosomal proteases such as MMPs, A Disintegrin And Metalloproteases (ADAMs) and the related A Disintegrin with thrombospondin motifs (ADAMTs), and mechanistic insights into their roles within the tumor microenvironment. Bronger et al. report that proteolysis of chemokines is an important regulator of lymphocytic infiltration in solid tumors. Given the increasing reliance on immune-based therapies in contemporary cancer treatment, this is also a critical process that warrants further examination. Liyanage et al. describe yet another regulatory process, alternative splicing at the mRNA level, that leads to various protease isoforms, such as those associated with the cathepsins, caspases, ADAMs, and KLK serine proteases. Such splicing events lead to isoforms that regulate the pro-/anti-apoptotic activities of caspases and modify the intra- and extra-cellular action of the

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cathepsins and ADAM proteases, respectively, thus also impacting on tumor signaling processes.

Finally, we have two reviews that focus on inhibitors of key proteolytic pathways, the tissue inhibitor of metalloproteinase (TIMP) family and plasminogen activator inhibitor 1 (PAI-1). Eckfeld et al. suggest that the functional disparities observed within the TIMP family in cancer progression, that is pro-tumorigenic effects in their own right as well as inhibition of MMP pro-tumorigenic action, may be explained by molecular analysis of the TIMP interactome. Similarly, Kubala and DeClerck, suggest that a better mechanistic understanding of the structural features of PAI action may help to better understand the multifaceted action of PAI-1 in the tumor microenvironment.

Overall, these authors have given us insight into the key roles, both intra- and extra-cellular, of proteases of many different classes and their impact on the tumor microenvironment in both localized disease and metastatic progression. Notably, the impact of new technologies and concepts, as described herein, has advanced the field enormously in the past few years and will continue to do so in the short term. Such insights may lead in the near future to novel drug targets that disrupt key proteolytic events in cancer progression and metastasis.