Perspectives on molecular signaling in cancer and update on therapeutic options for the treatment of metastatic cancer

As guest editor of this special series of the *Annals of Translational Medicine* (*ATM*), I would like to share with the readers at large the contributions from invited authors who provided their unique and expert perspectives on the important and critical topics of this focus series titled "Cancer Metastasis: Molecular signaling and therapeutic options". According to the latest data released by the world health organization, cancer is the second leading cause of death globally, accounting for almost 10 million deaths. In 2018, one in six deaths were caused by cancer. While Lung cancer is leading the death toll in both men and women, breast cancer is the most diagnosed cancer and second cause of death in women. The burden of cancer continues to grow globally and exerts significant physical, emotional and financial strain on individuals, families, communities and health systems. This burden is even higher in low- and middle-income countries, where health systems are least prepared to manage this stress-causing burden. Survival rates in cancer patients are however higher in countries where health systems are strong, compared to low and middle-income countries, thanks to easy access to early detection, treatment quality and survivorship care. In addition, and regardless of the economic status of the country of origin, a significant number of cancer patients still does not have access to good quality diagnosis and treatment, even in industrialized countries, therefore, highlighting the fact that cancer is a problem that is not unique to industrialized nations (1). Accordingly, this special series of the ATM provides perspectives on cancer not only in the United States (US), but also worldwide. We present a global, comprehensive view of innovative research, and reviews from basic science at the bench level to clinic interventions and public health considerations. This edition of ATM builds on much of the research and clinical care conducted by authors from the USA, along with articles from basic science researchers, clinicians and public health specialists from Europe and Asia.

The acquisition of the metastatic phenotype is responsible for the death of ~90% of breast cancer (BC) patients (2). In fact, metastatic BC is the 2nd leading cause of cancer-related deaths in women in the United States, annually accounting for more than 41,000 deaths and 260,000 new cases of invasive BC (2). Typically, metastases are incurable and result in a median survival of only 1.5 to 3 years for BC patients. Clinically, ~30% of BC patients diagnosed with early-stage, noninvasive disease will ultimately progress to late-stage, metastatic disease, an event that severely limits treatment options and associates with dismal clinical outcomes (3). This problem is exacerbated by the fact that BCs are heterogeneous and comprised of at least 5 genetically distinct subtypes (4-7). Amongst individual BC subtypes, those classified as triple negative BCs (TNBCs) are especially lethal due to their highly metastatic behavior and propensity to recur rapidly (6,7). As a group, TNBCs lack expression of hormone receptors (ER-α and PR) and ErbB2/HER2, which has prevented the development of FDA-approved targeted drug therapies effective against this BC subtype. Likewise, recurrent TNBCs frequently acquire resistance to standard-of-care chemotherapeutic agents (e.g., doxorubicin, cyclophosphamides, and taxanes) through mechanisms that remain incompletely understood. The reviews by Kansakar *et al.* describes how WAVE3 functions as a major driver of the invasion-metastasis cascade. WAVE3 is a member of the WASP/WAVE family of actin-cytoskeleton remodeling proteins (8,9), and plays an essential role in the regulation of cancer cell migration and invasion, through the regulation of the EMT program (10,11). The oncogenic activity of WAVE3 is also driven by its regulation and maintenance of the cancer stem cell (CSC) subpopulation in TNBC tumors (12). The activity of WAVE3 in cancer cells is also driven by phosphorylation downstream of PI3K, and that this post-translational modification enhances the WAVE3-mediated activation of cancer cell properties, including the activation of tumor growth, invasion, metastasis, and resistance to standard of care therapies (13). The review by Kansakar and colleagues discusses the recent literature highlighting the role of WAVE3 as major player in the oncogenesis of TNBC and other cancer types by regulating several hallmarks of cancer.

Kindlin-2 (K2) has been characterized as a novel regulator of metastatic progression and disease recurrence in cancer (14-16). Kindlins are a small gene family (3 members) of FERM domain-containing adaptor proteins that function as essential drivers of integrin activation (17-19). Moreover, aberrant Kindlin expression and activity is associated with several human pathologies, including cancer (17,18). K2 is the most widely expressed member of the Kindlin family; its homozygous deletion in mice is embryonic lethal, while mice heterozygous at the K2 locus exhibit overtly normal phenotypes that give way to defects in angiogenesis, hemostasis, and the cytoskeletal architecture upon stress induction (19). K2 expression is also

dysregulated in several human cancers, including those originating in the breast. The review by Wang *et al.*, provides an extensive update on the molecular mechanisms involving K2 in the activation of cancer cell behavior, and how therapeutic targeting of K2 my prove to be beneficial for the treatment of cancer.

One of the hallmarks of cancer is the activation the invasive phenotype of cancer cells (20,21). Cancer cells acquire this invasive property in part through the formation of invadopodia structures or invadosomes, which are developed as cell membrane protrusions composed mainly of F-actin fibers and lipid rafts, but also contain a plethora of enzymatically active proteins (22). Invadopodia are very specialized structures with enhanced proteolytic activities that allow the degradation of the extracellular matrix (ECM) at the contact interface between the ventral surface of cancer cells, which is also enriched in adhesive structures like focal adhesions, and the ECM (23). The proteolytic and degradative activities of invadopodia are believed to play a major role in driving the invasion and metastasis of cancer cells (24,25). The review by Augoff *et al.* provide an in-depth analysis of how the formation and activity of invadopodia are regulated and how invadopodia regulate cancer cell invasion.

As noted above, our current understanding of how BCs become metastatic remains poor, as does our knowledge of how disseminated BCs escape clinical detection by remaining latent for years before reemerging as chemoresistant and incurable secondary tumors. Indeed, the mysteries of metastatic latency have been identified as 1 of the 10 most critical research gaps and translational priorities needed to be solved to alleviate BCs. Detecting disseminated malignancies has always been a big challenge and is highlighted by the fact that analysis of the majority of post-mortem pathology of trauma patients identified undiagnosed micrometastatic lesions (26,27), implying that dormant BC micrometastases play a pivotal role in the majority of BC-associated mortalities. The manuscript by Schiemann *et al.* discusses the role that cancer dormancy and the epigenetic-mediated regulation of dormancy play in cancer pathology, progression and metastasis.

Meanwhile, the manuscript by Yu *et al.* is a comprehensive review of emerging concepts on the role of mitochondrial metabolism in cancer metastasis. The mitochondrial system, in addition to its known status as the power generator for the body, recent data have also found the mitochondrion to be critical for several metabolic functions, such as oxidative phosphorylation, β-oxidation of fatty acids, tricarboxylic acid cycle, calcium handling, proline synthesis, and heme biosynthesis. Accordingly, dysregulation of the mitochondrial metabolic activities has been associated with several metabolic diseases, as well as cancer (28-30). Yu and colleagues discuss how mitochondrial metabolites derivatives and how mitochondrial metabolic plasticity, by adapting to anabolic functions can play a major role in driving oncogenesis and cancer metastasis. This review also highlights how mitochondrial metabolism can be a promising target for novel anticancer therapies.

The focus of the review by Horowitz *et al.*, on the other hand, is entirely dedicated to epithelial ovarian cancer (EOC) and potential treatment modalities for this type of cancer which is yet another devastating cancer to women at different stages of their lives (31). In 2020, it was estimated that more than 60,000 women will lose their lives to EOC (2). Standard of care treatments for EOC, like in TNBC, are still relying on the cytotoxic platinum-based chemotherapies, with very low response rate, mainly because of early disease recurrence and the development of chemoresistance, therefore, accounting for the overall poor outcome and survival rate (32,33). In this review, the authors discuss how the interplay between the different tumor components and the tumor microenvironment drives the chemoresistance phenotype of EOC. The authors also discuss the multitude of cellular and molecular pathways driving the chemoresistance phenotype as well summarizes the ongoing clinical trials that are currently available to patients with EOC.

New advances in screening and treatment strategies in breast cancer (BC) has led to a significant decline in breast cancer-related mortality over that past 30 years. However, the improved outcome has not proven to be equitably distributed across the diverse populations world-wide (34). In the United States, specifically, the mortality rate within African American (AA) women is significantly higher (20% to 50%) compared to their European American (EA) counterparts (3,35), therefore, highlighting the deep problem of cancer health disparities between these two populations. This disparity in BC incidence and outcome is further higher in AA women with TNBC, where the probability of being diagnosed with TNBC is more than double in AA than in EA women (36). Furthermore, even though the TNBC represent less than 20% of all BC subtypes (4,5), the incidence rate of TNBC accounts for almost 50% of all BCs in AA (37). The review by Varadan *et al.* discusses how the interplay between the patients' socioeconomic status and the biology of their tumors contributes the health disparities in AA with TNBC.

Finally, Abraham *et al.* provide an in-depth perspective and an update of the therapeutic options that are currently available to patients with metastatic breast cancer and their impact on the patient survival. In addition to the traditional standard of care therapies, the authors also discuss the utility and efficacy of novel targeted and personalized therapies for patients that fail to respond to standard of care therapies.

The authors hope that these reviews will provide new and helpful information to readers with expertise in basic, translational and clinical cancer research, with special interest in metastatic cancer.

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