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PREFACE

TGFβ Biology in Breast: 15 Years On

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It is a pleasure to introduce the Journal of Mammary Gland Biology and Neoplasia issue on transforming growth factor β (TGFβ) biology, in large part because it affords reflection on the 15 years of research since the TGFβ issue in the first year of the journal. At that time, TGFβ was recognized more for its regulation of normal epithelial proliferation, stimulated by the seminal studies by Daniel and Silberstein using the mammary gland to demonstrate its potency in vivo. Even so, studies from Knabbe, Arteaga, Lippman, Dickson and others in breast cancer cells had already begun to hint at the now well-recognized TGFβ paradox.

TGFβ was first discovered more than a quarter of a century ago as the founder of a large family of 'transforming growth factor' polypeptides involved in all aspects of development, homeostasis and cancer (reviewed in [1]). The activity of TGFβ was first implicated in mammary epithelial development in 1987 by a canonical experiment by Daniel and Silberstein. Pellets containing TGFβ implanted into mouse mammary gland during ductal morphogenesis were shown to induce rapid regression of advancing endbuds, which was among the first demonstration of potent inhibitory, rather than transforming, activity [2]. The same year, work from NCI investigators showed that breast cancer cells also produce TGFβ, which in turn contributed to resistance to hormone therapy [3]. Thus, TGFβ orchestrates critical events during mammary development via its growth regulatory functions and mediation of microenvironment composition but it is subverted during cancer progressively to actively drive malignancy. Almost all breast cancers evade growth control via a complex route, rather than mutational inactivation, because they exploit the dark side of TGFβ biology: invasion, motility, and self-renewal within the cancer and immunosuppression and recruitment /induction of pro-tumorigenic host cell phenotypes.

Is it surprising that the biology of TGFβ in normal mammary gland and breast is still being defined? There are many proteins that regulate TGFβ activity or mediate specific pathways and their explicit consequences have yet to be incorporated into the mammary lexicon. Studies from my laboratory have attempted to assess the contribution of stromal versus epithelial TGFβ and the effects of radiation using the unique capacity of assembling disparate compartments into a functional mammary gland. The mammary chimera developed by DeOme and colleagues [4], in use for over a half a century, has been a marvelous tool for breaking down complex processes. Serra and colleagues also use this technique in their studies of the role of Wnt5A, an effector of TGFβ signaling, whose actions in the mammary gland include roles in mammary branching during morphogenesis. Notably Wnt5A links TGFβ with β catenin antagonism that is critical in stem cell regulation; moreover its dysregulation is repurposed during progression to mediate metastasis. TGFβ chaperones, called latent TGFβ binding proteins (LTBP), are critical to localization, function and activity. Cowin and colleagues review their potential importance in the mammary gland development, which is understudied, and raise the interesting idea that LTBPs may be structural bridges mediating malignant behaviors in metastasis.

The so-called TGFβ paradox is still being untangled. What has become clearer is how TGFβ signaling pathways are intertwined with other important signal in breast cancer. TGFβ is one of the most commonly altered cellular

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signaling pathways in human cancer. The contributions to this issue dissect important interplay between TGFβ and oncogenic events. TGFB1 polymorphisms appear to play a role in cancer susceptibility and response but as is typical of TGFβ biology, the simple answer is that it is complicated. Moore-Smith and Pasche discuss the prevalence of TGFβ pathway mutations as potential tumor modifiers of cancer susceptibility in populations and the molecular underpinnings of the associations, which are still poorly understood. Chou et al. raise the issue in the context of HER2 overexpressing breast cancer as a determinent of TGFβ biology in that functional alterations in the anti-mitogenic effect from Smad-mediated transcription cooperates with gain of pro-survival and pro-migratory function through HER2-dependent mechanisms. Band and Laiho discuss the implications of the critical intersection of TGFβ signaling and estrogen receptor signaling in breast cancer as well as the implications for anti-hormone therapies that remain underexplored.

TGFβ inhibitors are in clinical trials for many indications but have been contentious in breast cancer despite the clear evidence of TGFβ's powerful role in progression and metastasis. As discussed by Drabsch and ten Dijke, TGFβ involvement in crosstalk between the breast tumor cells and the microenvironment promotes bone or lung metastasis in part via effects on cancer cell plasticity. Likewise, Pavani, Taylor and Schiemann examine of the dynamics of canonical and noncanonical TGFβ signaling between distinct breast cancer subpopulations and the microenvironment during mammary carcinogenesis. The potential benefit of controlling TGFβ during cancer progression and in response to therapy may gain credence with growing appreciation that physiological action is highly localized and therapeutic inhibition can achieve benefit without significant toxicity [5].

Jerry and colleagues contrast the possibly 'pure' antitumorigenic effects of activins, another TGFβ family member, in the context of physiological factors that are strongly associated with breast cancer risk. This contribution underscores the complexity of TGFβ biology in the mammary gland and breast by reminding us that its extended family is very poorly studied to date. It would be a considerable undertaking to even begin to describe the dynamics of TGFβ family members' production, activity and consequences in toto, much less to understand the interactions among them and with other pathways.

The next 15 years, or perhaps 10, will hopefully give rise to much needed systems biology methods and models that synthesize information across the scales of organization and time. Systems biology is not just a comprehensive catalogue but also a framework in which interactions give rise to emergent properties, both physiological and pathological. Indeed one might call the mammary gland an ideal organ for a systems biology approach to not only link pathways, signals and events, but understand the time scale that ranges from embryogenesis through lactation, from mutations to metastasis.

Cover Legend

The Distribution of Latent and Active TGFβ in Mammary Gland Endbud A micrograph is shown of a cryosection from Balb/c mouse that has been immunostained with antibodies to latency associated peptide (green) and TGFβ (red) with nuclei counterstained with DAPI (blue). The distribution of latent TGFβ is broad and includes the epithelium, myoepithelium, periepithelial stroma and adipose stroma. The active form of TGFβ is highly restricted in contrast; primarily found in cells that are suprabasal or luminal [6].

References

1. Moses HL, Roberts AB. The discovery of TGF-β: a historical perspective. In: Derynck KRAM, editor. The TGF-β family. Cold Spring Harbor: Cold Spring Harbor Laboratory Press; 2008. p. 1–28.
2. Silberstein GB, Daniel CW. Reversible inhibition of mammary gland growth by transforming growth factor-β. Science. 1987;237:291–3.
3. Knabbe C, Lippman ME, Wakefield LM, et al. Evidence that transforming growth factor-beta is a hormonally regulated negative growth factor in human breast cancer cells. Cell. 1987;48(3):417–28.
4. Deome KB, Faulkin Jr LJ, Bern HA, et al. Development of mammary tumors from hyperplastic alveolar nodules transplanted into gland-free mammary fat pads of female C3H mice. Cancer Res. 1959;19(5):515–20.
5. Barcellos-Hoff MH, Akhurst RJ. Transforming growth factor-beta in breast cancer: too much, too late. Breast Cancer Res Treat. 2010;11(1):202–8.
6. Ewan KB, Shyamala G, Ravani SA, et al. Latent TGF-β activation in mammary gland: regulation by ovarian hormones affects ductal and alveolar proliferation. Am J Path. 2002;160(6):2081–93.