

VIEWPOINT

Unraveling the 'TGF- β paradox' one metastamir at a time

Danny R Welch*¹ and Douglas R Hurst²

Abstract

Transforming growth factor beta (TGF- β) has received noteworthy attention in the recent past due to its unique characteristic of functionally switching roles from tumor suppressor to metastasis promoter. To uncover the black box surrounding the mechanisms of TGF- β , Taylor and colleagues performed global miRNA expression analyses using a murine mammary carcinoma progression model. They discovered multiple miRNA regulated by TGF- β and matrix stiffness. Focusing on miR-181a, they uncovered an intricate pathway regulating breast cancer metastasis that sheds new insight into metastasis regulation that may prove useful in clinical settings.

One of the greatest disappointments in the war on cancer is that survival for patients with metastasis remains abysmal (much less than 25%), highlighting the dire need for improved treatment options. Metastasis is inexplicably complex, requires coordinated expression of multiple genes and proteins, and requires intricate communication of tumor cells to the constantly-changing environments as cells disseminate and colonize other tissues [1]. While the process is fortuitously inefficient, when cells succeed there are few effective treatment options. In addition to improving our clinical trial system [2], attention cannot be drawn away from the basic research that will unravel the cellular networks that drive metastasis.

Metastasis research has evolved in the past two decades. Early studies focused on individual genes or proteins that contribute to or inhibit the process. In the past few years, those individual metastasis-associated molecules are, not surprisingly, being assembled into coordinated pathways. Also, while researchers have long

recognized that metastatic cells interact with other cells, matrices and soluble molecules, roles of the micro-environment are becoming increasingly appreciated. Among myriad signaling molecules contributing to metastatic behavior is transforming growth factor beta (TGF- β).

A long-time, unsolved mystery in cancer biology is the paradoxical effect of TGF- β , which suppresses growth and tumorigenicity when cells are normal or near normal but somehow becomes a promoter of invasion and metastasis as neoplasms progress [3]. Both cell-autonomous and noncell-autonomous mechanisms have previously been invoked. In a recent publication by Taylor and colleagues [4], however, a new intermediary in the process has been uncovered. The results also highlight how microenvironment conditions, in this case matrix, are not inert bystanders in cellular behavior; and how the authors began the process of sorting through TGF- β -miRNA pathways that differentially mediate growth and invasive behaviors.

Launching from Weaver and colleagues' findings showing that tumor cells respond to matrix stiffness differentially [5] and that matrix rigidity – that often accompanies desmoplasia – differentially regulates TGF- β responses, the Schieman group grew breast carcinoma cells in two different matrices with a goal to mimic matrix tensegrity at primary tumors and metastatic sites [6]. Using three-dimensional cultures of mammary carcinoma cells treated with TGF- β in stiff or fractile matrices (Cultrex \pm type I collagen, respectively), differential responses were observed as expected. Global miRNA expression analyses were performed and a panel of metastasis-associated miRNA, so-called metastamir [7], was identified. They smartly focused on one miRNA, miR-181a, that was regulated in both tissue culture conditions and in three isogenic murine mammary carcinoma cell lines. The remainder of their studies characterized the role of miR-181a in promoting mammary cancer progression. Inhibition of miR-181a clearly altered lung colonization after tail vein injection. However, tumor latency, growth and dissemination did not appear to change (Note: the inhibition was lost in the tumor cells that successfully colonized, suggesting that they were revertants.) These

*Correspondence: dwelch@kumc.edu

¹Department of Cancer Biology, The Kansas University Medical Center, 3901 Rainbow Blvd, Wahl Hall West 2003, Mailstop 1071, Kansas City, KS 66160, USA
Full list of author information is available at the end of the article

findings further highlight how metastasis is a distinct phenotype from primary tumor growth.

As various laboratories dissect molecular mechanisms of metastatic spread, the identification of signaling pathways, including networks connecting matrices, signaling molecules and miRNA, is emerging. miRNA are increasingly recognized as key regulators of networks controlling normal cell functions and pathologies [8]. Progress has been slowed somewhat in defining miRNA since each miRNA can have as few as one or as many as hundreds of targets. Superimposing the intricate cellular interactions occurring throughout the metastatic process and the interconnectivity of miRNA in various signaling cascades, the complexity multiplies. Nonetheless, several themes begin to emerge.

We [9,10] and others [11,12] previously showed a metastasis suppressor–metastamir pathway; others have linked TGF- β signaling with miRNA that regulate epithelial–mesenchymal transition [13]; and, still others link miRNA as feedback to traditional signaling pathways [14]. As these networks become more finely elucidated, they are beginning to define metastasis mechanisms and patterns for particular molecular subtypes of cancer. Invoking miRNA represents an exciting avenue for translational studies since miRNA have taken center-stage in recent years as both biomarkers and directed therapy against cancer [15]. The miR-181a expression inversely correlated with patient survival, serving as a promising biomarker or therapeutic target. However, we urge caution with imposing findings on cancer subtypes at this time, since more extensively powered studies will be required to make firm such assertions.

While there is substantial promise, questions remain. How does matrix (composition or tensegrity) regulate TGF- β signaling? Do all of the miRNA changed by TGF- β work in concert? Are miRNA networks dependent upon the microenvironment? Are there bypass pathways or is there redundancy in miRNA pathways? How many of the other miRNA regulated by TGF- β also change growth or metastasis? Are there ways in which the microenvironment could be treated to induce the growth-suppressive TGF- β effects? These (and many other) questions will not be addressed in a single study. But tackling the pathways systematically (that is, one molecule at a time) may uncover networks that will translate into relevant personalized treatments.

Abbreviations

miRNA, micro RNA; TGF- β , transforming growth factor beta.

Competing interests

The authors declare that they have no competing interests.

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Author details

¹Department of Cancer Biology, The Kansas University Medical Center, 3901 Rainbow Blvd, Wahl Hall West 2003, Mailstop 1071, Kansas City, KS 66160, USA. ²Department of Pathology, University of Alabama at Birmingham, 1670 University Blvd, G019 Volker Hall, Birmingham, AL 35294, USA.

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