Discoidin Domain Receptor 2 (DDR2): an emerging player in breast cancer metastasis.

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Abstract : Metastasis is the predominant cause of poor prognosis in breast cancer patients and is thought to be driven, at least partly, by epithelial to mesenchymal transition (EMT) of tumor cells. Mechanisms that promote EMT are being investigated intensively as these may present novel opportunities for therapeutic intervention. Zhang et al have successfully identified a novel collagen dependent signaling pathway mediated via the Discoidin Domain Receptor 2 (DDR2) that contributes to EMT and metastasis in breast cancer. Their key observations and the therapeutic significance of their findings are discussed in this comment.

Keywords: breast cancer, epithelial to mesenchymal transition, SNAIL1, Discoidin Domain Receptor, metastasis, collagen, signaling

Epithelial to Mesenchymal Transition (EMT) is a key driver of breast cancer progression and metastasis [1, 2]. Several transcription factors, including SNAIL1, SLUG, TWIST1 and Zeb have been implicated in the induction of EMT [3]. In the case of SNAIL1, a differential expression pattern of mRNA and protein has been observed in primary tumors from patients, with mRNA expression generally present throughout the tumor and protein expression found predominantly at the tumor-stroma interface [4] . How SNAIL1 protein expression and hence EMT is maintained only at the tumor front is not very well understood. To address this question, Zhang *et al* previously conducted a short interfering RNA (siRNA) screen to identify regulators of total cellular SNAIL1 protein levels [5]. They identified Discoidin Domain Receptor 2 (DDR2), a novel receptor tyrosine kinase (RTK) that signals in response to stromal collagen, as one of the genes required to maintain cellular SNAIL1 protein levels. In the present study, they conducted a detailed analysis of the mechanism of DDR2-mediated SNAIL1 stabilization, thereby unraveling the novel role of collagen-mediated DDR2 signaling in breast cancer metastasis. Their exciting findings were recently reported in Nature Cell Biology [6].

Using the malignant human and mouse breast cancer cell lines, MDA-MB-231 and 4T1 respectively, Zhang *et al* demonstrate that modulating DDR2 levels alters SNAIL1 protein but not mRNA levels; downregulating DDR2 expression results in low SNAIL1 protein while upregulating DDR2 expression results high SNAIL1 protein levels. Surprisingly, however, other EMT transcription factors were either not affected or only slightly modulated, suggesting a SNAIL1-specific regulatory mechanism. While SNAIL1 alone is capable of inducing EMT in breast epithelial cells, DDR2 was neither necessary nor sufficient

for this process, indicating that DDR2, through its effects on SNAIL1 stability, plays a role in maintaining the mesenchymal, invasive state rather than in inducing it. Like SNAIL1, DDR2 was found to promote invasion *in vitro* and increase breast cancer lung metastasis in mice. To understand the mechanisms underlying DDR2-mediated SNAIL1 stabilization, Zhang *et al* went on to delineate the intracellular signaling pathway initiated by collagen-mediated DDR2 activation, leading to ERK2 activation, and subsequently, SNAIL1 phosphorylation. Phosphorylated SNAIL1 accumulates in the nucleus and is thereby protected from ubiquitylation and proteasomal degradation. Thus, they discovered that DDR2 activation at the tumor-stroma interface triggers a signaling pathway that results in nuclear SNAIL1 stabilization and consequently, sustained SNAIL1 activity.

This study shines the spotlight on DDR2 as a novel therapeutic target in breast cancer patients. Indeed this notion is strongly supported by recent molecular profiling studies that identified DDR2 as a gene that is significantly amplified in a large number of breast cancer patients [7]. Given the findings of Zhang and co-workers, one might speculate that DDR2 gene amplifications may play a role in increasing tumor invasiveness in these patients. Indeed, patients with DDR2 copy number aberrations have a much worse overall survival rate compared to those that don't [6]. Whether these effects are directly due to increased DDR2 expression and hence increased SNAIL1 stabilization and tumor metastasis is yet to be investigated.

DDR2 is unique among RTKs in that it is activated by fibrillar collagen rather than soluble growth factors (reviewed in [8]). Fibrillar collagen type I constitutes a major proportion of the stromal extracellular matrix (ECM), the remodeling of which, is essential for tumor migration, dissemination and subsequent metastatic events. Collagen fiber remodeling and realignment results in various "signatures" characteristic of non-invasive or invasive tumors [9]. Interestingly, Zhang *et al* observed in their experimental models, that tumors expressing DDR2 displayed a tumor associated collagen signature (TACS) characteristic of invasion (i.e., TACS3) while those that were depleted of either DDR2 or SNAIL1 displayed the non-invasive collagen signature (i.e., TACS2). How DDR2 influences collagen remodeling around tumors is not clear at present.

Given the abundant epidemiological evidence linking high collagen density/mammographic density and breast cancer incidence [10], it is tempting to speculate that DDR2 may be a key player in driving breast cancer progression in women with dense or fibrotic breasts. Future studies will likely highlight the importance of DDR2 as a novel diagnostic and prognostic marker in breast cancer patients while ongoing intense efforts to generate DDR2 specific kinase inhibitors will be instrumental in realizing the therapeutic potential of this novel target.

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