Published in final edited form as:

Sci Signal. ; 7(318): pe9. doi:10.1126/scisignal.2005236.

Flipping the Switch: Integrin Switching Provides Metastatic Competence

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Abstract

Integrin switching plays a critical role in the progression to metastatic disease, but the mechanism by which it contributes remains poorly understood. In the 11 February 2014 issue of *Science Signaling*, Truong *et al.* identified a transforming growth factor- β -mediated, prometastatic switch that is activated by $\beta 1$ integrin inhibition in triple-negative breast cancers (TNBCs). Their work provides insight into the complex signaling changes that arise from integrin switching. Further characterization of β -integrin switching will require elucidation of the distribution of specific α - β integrin heterodimers and the role of ligand binding. Identifying the nature of the molecular interactions and the influence of a specific oncogenic context, including the status of driver mutations such as those in *Myc* and *p53*, will define the next phase in integrin cancer biology.

Malignant progression of cancer is supported largely by cues received through altered cell-cell and cell-matrix interactions that promote the metastatic potential of malignant cells. Integrins, a class of cell-surface adhesive receptors that exist as obligate α - β heterodimers, mediate many of these interactions (1). Oncogenic transformation can directly or indirectly increase the abundance of certain integrin subunits and decrease that of other integrin subunits, thereby changing not only the absolute number of available integrins but also their α - β composition. Consequently, the integrin repertoire is changed or “switched” to support cancer initiation and progression. In many instances, integrins that secure adhesion to the basement membrane are lost, whereas the abundance of integrins that stimulate cell survival, migration, proliferation, and invasion are increased. Although the specific nature of integrin switching varies among cancers, $\alpha 2 \beta 1$ and $\alpha 3 \beta 1$ integrins suppress cancer progression and metastasis, whereas $\alpha 5 \beta 1$ and $\beta 3$ and $\beta 4$ integrins can promote metastatic progression (1, 2). Integrin switching is central to epithelial-mesenchymal transition (EMT), a process in which polarized epithelial cells transition to a migratory mesenchymal-like state during malignant progression. However, the mechanism by which integrin switching contributes to metastatic progression remains poorly understood.

The $\beta 1$ integrin subunit pairs with at least 11 α subunits to produce heterodimers that mediate adhesion to a wide variety of ligands, including matrix molecules (such as collagen, laminin, and fibronectin, among others) and cell surface proteins, such as E-cadherin and

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Competing interests: The authors declare that they have no competing interests.

vascular cell adhesion molecules (1). Studies using in vitro and in vivo orthotopic or xenograft models indicate that the $\beta 1$ integrins mediate drug resistance and stimulate metastasis in gastric, ovarian, and lung cancers (1). Similarly, animals with targeted deletion of the $\beta 1$ -encoding gene in mammary epithelium fail to develop cancer, suggesting that the $\beta 1$ integrins are essential for cancer initiation (3). However, the loss of specific $\beta 1$ integrin species may be important in progression to metastasis. Transgenic deletion of $\alpha 2\beta 1$ integrin increases metastasis in the spontaneous MMTV-Neu tumor model, whereas the loss of $\alpha 3\beta 1$ promotes metastasis in models of prostate cancer (2, 4). Decreased abundance of these $\beta 1$ species in human patients affirms their clinical relevance in disease progression. Consequently, understanding how the loss of $\beta 1$ integrin functions contributes to metastatic progression has both mechanistic and therapeutic implications.

In the 11 February 2014 issue of *Science Signaling*, Truong *et al.* reported that functional inhibition or knockdown of the $\beta 1$ integrin enhanced metastatic lung colonization by promoting EMT through activation of the transforming growth factor- β (TGF- β) signaling network (Fig. 1A). This converted the migratory behavior of human and mouse triple-negative breast cancer cells (TNBCs) from collective to single-cell movement and enhanced metastatic lung colonization by decreasing the expression of the gene encoding E-cadherin through a pathway involving microRNA-200 (miR-200) and the transcription factor ZEB2 (5).

These intriguing results are reminiscent of findings from Parvani *et al.* who observed a compensatory increase in $\beta 3$ integrin expression upon $\beta 1$ integrin inhibition in breast cancer (6) (Fig. 1B). However, whereas Parvani *et al.* suggested that $\beta 3$ integrin overexpression alone was sufficient to mediate metastatic competence, Truong *et al.* found $\alpha 3$ integrin overexpression to be insufficient for TGF- α -induced metastasis in their model. Interestingly, Truong *et al.* observed that inhibition or knockdown of $\alpha 1$ integrin governed a trade-off between tumor cell proliferation and cell motility and dissemination, leading to reduced growth at both the primary and secondary locations while promoting systemic dissemination. Those findings reaffirm the well-established requirement of proliferative signals from $\alpha 1$ integrin and highlight the integration of proliferation and migration. The correlation to a $\alpha 1/\alpha 3$ switch to this behavior was also observed by Liu *et al.*, who found that Myc overexpression supported tumor proliferation but not invasion and motility because of repressed expression of the gene encoding $\alpha 3$ integrin (7). Together, these findings indicate that both loss of $\alpha 1$ integrin and gain of $\alpha 3$ integrin are required to provide metastatic competence.

Observations by Truong *et al.* suggest that integrins are potent therapeutic targets in our attempts to counter the proliferative and invasive signals. However, it will be important to consider the balance of signal integration through $\alpha 1$ and $\alpha 3$ because simply inhibiting either alone could inadvertently drive dissemination or tumor growth.

These findings also offer a new perspective on the influence of integrin switching in EMT and tumor metastasis. TGF- α famously plays a dichotomous role in cancer, acting as a tumor suppressor in early carcinomas and a promoter of EMT and metastasis in more advanced cancers. Perhaps integrin switching from $\alpha 1$ to $\alpha 3$ integrin directs the biological

response to activation of the TGF- α signaling network. Although conclusive evidence is not yet available, matrix interactions are clearly relevant as Leight *et al.* have recently demonstrated that matrix rigidity regulates the phosphoinositide 3 kinase/AKT-dependent switch between TGF- α -induced apoptosis and TGF- α -induced EMT (8). Additionally, direct interaction between TGF- α and both $\alpha 1$ and $\alpha 3$ integrins have been documented, indicating the potential for differential complex-specific signaling (6).

Truong *et al.* observed that $\alpha 1$ integrin inhibition potentiated TGF- α -induced EMT only in TNBC. As TNBCs present clinically with a high incidence of lymph node metastasis even among small tumors, the trade-off between proliferation and metastasis may explain an important aspect of TNBC biology. New TNBC subclassification schema proposed by Lehman *et al.* may help to further identify the specific oncogenic contexts where Truong's integrin-TGF- α prometastatic switch may be relevant (9). Although there are several distinct properties that define the aggressive nature of TNBC, it is known to have particularly high p53 mutation status. Mutant p53 promotes both random cell motility and increased invasiveness by accelerating the recycling of $\alpha 1$ integrins to the plasma membrane, where the integrin complex may serve as a metastatic engine (10, 11). Upon phosphorylation, wildtype p53 binds Smads to support cytostatic TGF- α signaling. In contrast, complexes formed between mutant-p53 and Smads inhibit p63, a p53 family member that inhibits TGF- α -induced metastasis (12). Integration of the integrin-TGF- α prometastatic switch with p53 status may explain the divergent cellular response to TGF- α and thus warrants closer scrutiny.

In summary, the work of Truong *et al.* provides a mechanism by which loss of $\alpha 1$ integrin elicits a prometastatic switch in later stages of disease progression. Further characterization of α -integrin switching will require elucidation of the specific β - α integrin heterodimer distribution and the role of ligand binding. Identifying the nature of the molecular interactions and the influence of a specific oncogenic context, including the status of driver mutations, such as those in *Myc* and *p53*, will define the next phase in integrin cancer biology.

Acknowledgments

Funding: Research by the authors is supported by the National Institutes of Health (CA143081, CA098027, and CA133230).

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Fig. 1. Taking sides: integrin switching controls signaling output from the TGF- β network (A) $\beta 1$ integrins provide proliferative and cell survival signals that are critical for tumor growth. Early in tumor progression, $\beta 1$ integrins modulate TGF- β signaling to suppress its capacity for metastatic signaling. (B) In TNBCs, loss of $\beta 1$ integrins and gain of $\beta 3$ integrins enables a switch in TGF- β signaling, to inhibit the microRNA miR-200, and enable ZEB2 to suppress the expression of *CDH1* that encodes E-cadherin. The integrin-TGF- β switch ultimately leads to EMT, individual cell migration, and metastasis.