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J Rare Dis Res Treat. Author manuscript; available in PMC 2016 October 11.

Published in final edited form as:

J Rare Dis Res Treat. 2016 ; 1(1): 43–45.

Commentary: Activin and TGFβ use diverging mitogenic signaling in advanced colon cancer

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The TGFβ superfamily of ligands is defined by sequence homologies and consists of multiple members including TGFβ1, TGFβ2, TGFβ3, Activin A, Activin B, Activin AB, Nodal and BMPs (bone morphogenic protein)[1]. Signaling starts with ligand binding to a type II receptor, a serine/threonine receptor kinase, which catalyzes the phosphorylation of the associated type I receptor[2,3]. Each class of ligand binds to a specific type II receptor. TGFβ1 has a high affinity to the type I and type II receptor, whereas Activins are more promiscuous and are also able to bind BMP receptor type I[4].

Activin A is an under-appreciated member of the TGFβ superfamily of cytokines and its role in disease processes is often overshadowed by its well-studied big brother TGFβ. Activin A signaling is a critical pathway in development and its disruption can lead to significant disease. For example, mutation in the Activin receptor ACVR1, also known as ALK2 (activin receptor like kinase 2) can lead to different diseases. Somatic disruption of both the Activin A[5] and TGFβ1 signaling pathways[6] occurs frequently in colorectal cancers underscoring their importance in disease processes.

Colorectal cancer (CRC) incidence and mortality is declining due to enhanced screening resulting in early detection and interventions. However, mortality from metastatic disease remains high because prediction of metastasis is inaccurate and treatments ineffective. Alarmingly, more patients under the age of 40 years are presenting with metastatic disease[7].

While the TGFβ superfamily is tumor suppressive in the early transition from normal tissue to colon cancer, this role shifts in later stage more aggressive cancers to a metastatic role. In early stage CRC, the TGFβ superfamily is growth suppressive, while in advanced disease, high levels of TGFβ in the serum and stroma tissues are associated with poor prognosis[8,9]. Furthermore, Activin A in serum of CRC patients is increased compared to healthy controls[10]. Although Activin A and TGFβ1 utilize ligand specific membrane receptors to initiate signaling, these pathways were once thought to be redundant as they utilize identical SMAD-dependent canonical signaling downstream of their respective receptors[11]. Following binding of ligands to their primary receptor, phosphorylation of the secondary receptor leads to activation of the SMAD2/3 signal transduction molecules. These then translocate from the

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cytoplasm to the nucleus where they interact with a myriad of transcriptional coregulators to modulate target gene expression resulting in decreased cellular proliferation (Figure 1)[2]. However, both Activin A and TGFβ1 also signal in a non-canonical SMAD-independent fashion through signaling cascades such as MEK/ERK and PI3K. BMPs in contrast signal through SMAD1/5/8[4] and are not thought to play an important role in CRC.

The current key challenge regarding CRC detection and treatment consists in understanding the biology which promotes the switch to a metastatic phenotype and further to elucidate the signaling pathways which underly these processes in order to identify targets which may directly promote metastatic behavior. Because of the dual nature of Activin A and TGFβ1 actions, therapeutic targeting is especially complex as one needs to be certain not to abolish their protective antiproliferative responses if still operative.

Ultimately, given their importance in metastatic disease, both Activin A and TGFβ1 pathways are attractive putative targets. Despite several studies investigating TGFβ1 blockade in the setting of solid tumors including CRC, no benefit has been shown[12] to date. This might be due to the complex interplay of TGFβ1 with other pathways, such as Activin A, and the multifunctional character, where inhibition could theoretically not only lead to beneficial anti-metastatic effects, but simultaneously have detrimental effects of loss of growth suppression at least in a subset of patients. Unlike breast cancer which has clear treatment options based on the presence of biomarkers of signaling activity such as the estrogen receptor, the progesterone receptor and Her2[13], there are currently no decisive biomarkers to assess functionality of the TGFβ superfamily signaling pathways in CRC. Recently, we reported that in an APC (adenomatous polyposis coli) driven murine model of CRC global inhibition of TGFβ signaling leads to an autoimmune response, wasting and shorter survival[14]. Therefore, caution is warranted with regards to TGFβ1 inhibition in unselected CRC patient cohorts. In CRC biomarkers identifying patients with disrupted TGFβ1 signaling and a better understanding of pathway interconnectedness are needed before we can fully envision treatment strategies.

In that vein, we previously demonstrated that both Activin A and TGFβ1 signal via SMAD-dependent pathways to up-regulate expression of the cell cycle inhibitor p21 at early time points and further identified p21 as a predictor of net upstream Activin A and TGFβ1 pathway signaling both in vitro and in patient samples[15]. To understand the non-canonical mechanisms of p21 regulation in CRC, in Bauer et al.[16], we observed that at later time points, both Activin A and TGFβ1 induce migration and epithelial to mesenchymal transition (EMT) in a SMAD4 independent manner (Figure 1). Interestingly TGFβ and Activin diverge in their non-canonical signaling by utilizing MAP/ERK or PI3K signaling respectively. These data imply that in SMAD4 mutated CRC Activin and TGFβ1 non-canonical signaling promotes a metastatic phenotype. The net effect of Activin A signaling leads to down-regulation of p21 and an enhanced metastatic phenotype as measured by increased EMT. Similarly, TGFβ1 induced EMT results from down-regulation of p21 even when a more metastatic phenotype was measured independent of the canonical pathway. These somewhat surprising data indicate that p21 in isolation may be insufficient as a marker of metastatic potential in CRC, however may be used to understand dominance of upstream Activin A or TGFβ1 signaling, which we further validated in a primary cohort

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from CRC patients. While the disruption of SMAD-dependent signaling for Activin A and TGFβ1 was previously interpreted as complete loss of these pathways we believe that loss of SMAD-dependent signaling funnels Activin A and TGFβ1 signaling into the non-canonical pathways associated with a metastatic phenotype evidenced by increased migration and EMT.

We have additional evidence that the role of Activin A in metastatic disease is underappreciated. Activin signaling appears to be an equal participant in TGFβ superfamily pathway signaling with no lesser effects than TGFβ1. While TGFβ-directed therapeutics are clearly not appropriate for all CRC patients, there are sub-populations which would benefit from this approach. Activin A-directed therapeutics are not yet available. To implement this approach, biomarkers to stratify patients are needed and we propose that p21 localization could be such a biomarker. We support a novel view of Activin A as a co-conspirator with TGFβ1 in a closely interconnected system, with net Activin A and TGFβ1 signaling promoting metastasis. The mechanistic understanding of the Activin/TGFβ cross-regulation together with the translational component is highly significant and it shows great promise to improve clinical care for CRC patients in the near future under the provision of biomarkers in these patients.

Acknowledgments

This work was founded by the National Institutes of Health grant R01CA141057 to BJ. JJS was supported through a grant from the German Research Foundation (STA 1458/1-1).

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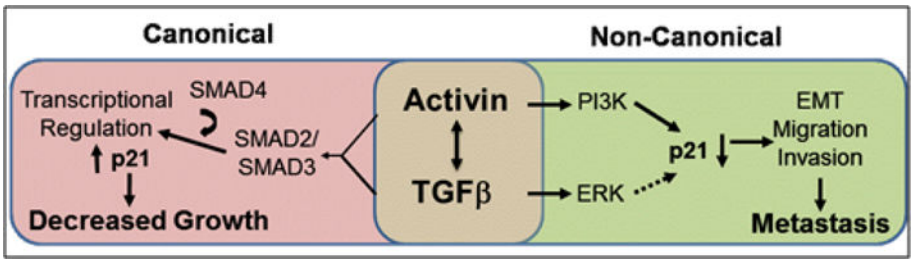

Figure 1. Schematic of proposed combined Activin and TGFb signaling

Dominant signaling through the canonical pathways favors increased p21 resulting in decreased cell growth. However, dominant signaling through the non-canonical pathways leads to a decrease in p21 and parallel unopposed stimulation of prometastatic epithelial mesenchymal transition (EMT), migration and invasion[11].