

## Commentary: Activin and TGF $\beta$ use diverging mitogenic signaling in advanced colon cancer

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### Article Info

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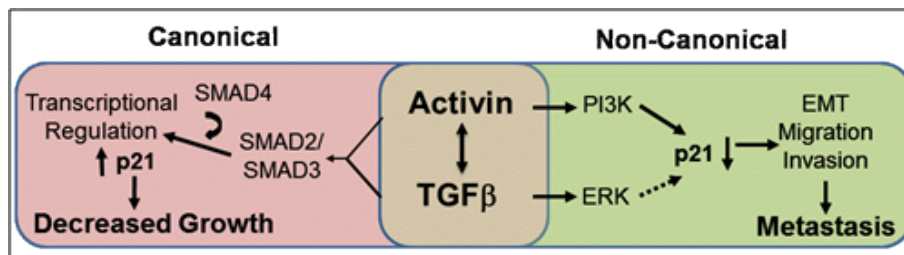
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The TGF $\beta$  superfamily of ligands is defined by sequence homologies and consists of multiple members including TGF $\beta$ 1, TGF $\beta$ 2, TGF $\beta$ 3, Activin A, Activin B, Activin AB, Nodal and BMPs (bone morphogenic protein)<sup>1</sup>. 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<sup>2,3</sup>. Each class of ligand binds to a specific type II receptor. TGF $\beta$ 1 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<sup>4</sup>.

Activin A is an under-appreciated member of the TGF $\beta$  superfamily of cytokines and its role in disease processes is often overshadowed by its well-studied big brother TGF $\beta$ . 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<sup>5</sup> and TGF $\beta$ 1 signaling pathways<sup>6</sup> 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<sup>7</sup>.

While the TGF $\beta$  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 TGF $\beta$  superfamily is growth suppressive, while in advanced disease, high levels of TGF $\beta$  in the serum and stroma tissues are associated with poor prognosis<sup>8,9</sup>. Furthermore, Activin A in serum of CRC patients is increased compared to healthy controls<sup>10</sup>. Although Activin A and TGF $\beta$ 1 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<sup>11</sup>. 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 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)<sup>2</sup>. However, both Activin A and TGF $\beta$ 1 also



**Figure 1: Schematic of proposed combined Activin and TGF $\beta$  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<sup>11</sup>.

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<sup>4</sup> 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 TGF $\beta$ 1 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 TGF $\beta$ 1 pathways are attractive putative targets. Despite several studies investigating TGF $\beta$ 1 blockade in the setting of solid tumors including CRC, no benefit has been shown<sup>12</sup> to date. This might be due to the complex interplay of TGF $\beta$ 1 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<sup>13</sup>, there are currently no decisive biomarkers to assess functionality of the TGF $\beta$  superfamily signaling pathways in CRC. Recently, we reported that in an APC (adenomatous polyposis coli) driven murine model of CRC global inhibition of TGF $\beta$  signaling leads to an autoimmune response, wasting and shorter survival<sup>14</sup>. Therefore, caution is warranted with regards to TGF $\beta$ 1 inhibition in unselected CRC patient cohorts. In CRC biomarkers identifying patients with disrupted TGF $\beta$ 1 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 TGF $\beta$ 1 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 TGF $\beta$ 1 pathway signaling both in vitro and in patient samples<sup>15</sup>. To understand the non-canonical mechanisms of p21 regulation in CRC, in Bauer et al.<sup>16</sup>, we observed that at later time points, both Activin A and TGF $\beta$ 1 induce migration and epithelial to mesenchymal transition (EMT) in a SMAD4 independent manner (Figure 1). Interestingly TGF $\beta$  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 TGF $\beta$ 1 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, TGF $\beta$ 1 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 TGF $\beta$ 1 signaling, which we further validated in a primary cohort from CRC patients. While the disruption of SMAD-dependent signaling for Activin A and TGF $\beta$ 1 was previously interpreted as complete loss of these pathways we believe that loss of SMAD-dependent signaling funnels Activin A and TGF $\beta$ 1 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 TGF $\beta$  superfamily pathway signaling with no lesser effects than TGF $\beta$ 1. While TGF $\beta$ -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 TGF $\beta$ 1 in a closely interconnected system, with net Activin A and TGF $\beta$ 1 signaling promoting metastasis. The mechanistic understanding of the Activin/TGF $\beta$  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.

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