



REVIEW

Recent advances in understanding contextual TGFβ signaling [version 1; referees: 2 approved]

Arshad Ayyaz¹, Liliana Attisano², Jeffrey L Wrana ^{1,3}

¹Center for Systems Biology, Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, ON, Canada

²Department of Biochemistry and Donnelly Centre, University of Toronto, Toronto, ON, Canada

³Department of Molecular Genetics, University of Toronto, Toronto, ON, Canada



v1 **First published:** 26 May 2017, 6(F1000 Faculty Rev):749 (doi: 10.12688/f1000research.11295.1)
Latest published: 26 May 2017, 6(F1000 Faculty Rev):749 (doi: 10.12688/f1000research.11295.1)

Abstract

The appearance of the first animal species on earth coincides with the emergence of transforming growth factor β (TGFβ) pathways. The evolution of these animals into more complex organisms coincides with a progressively increased TGFβ repertoire through gene duplications and divergence, making secreted TGFβ molecules the largest family of morphogenetic proteins in humans. It is therefore not surprising that TGFβ pathways govern numerous aspects of human biology from early embryonic development to regeneration, hematopoiesis, neurogenesis, and immunity. Such heavy reliance on these pathways is reflected in the susceptibility to minor perturbations in pathway components that can lead to dysregulated signaling and a diverse range of human pathologies such as cancer, fibrosis, and developmental disorders. Attempts to comprehensively resolve these signaling cascades are complicated by the long-recognized paradoxical role the pathway plays in cell biology. Recently, several groups have probed examples of the disparate aspects of TGFβ biology in a variety of animal models and uncovered novel context-dependent regulatory mechanisms. Here, we briefly review recent advancements and discuss their overall impact in directing future TGFβ research.

Open Peer Review

Referee Status:  

	Invited Referees	
	1	2
version 1 published 26 May 2017		

F1000 Faculty Reviews are commissioned from members of the prestigious F1000 Faculty. In order to make these reviews as comprehensive and accessible as possible, peer review takes place before publication; the referees are listed below, but their reports are not formally published.

- 1 **Harold L Moses**, Vanderbilt-Ingram Cancer Center, Nashville USA
- 2 **Peter ten Dijke**, Leiden University Medical Center Netherlands

Discuss this article

Comments (0)

Corresponding authors: Liliana Attisano (liliana.attisano@utoronto.ca), Jeffrey L Wrana (wrana@lunenfeld.ca)

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

How to cite this article: Ayyaz A, Attisano L and Wrana JL. **Recent advances in understanding contextual TGF β signaling [version 1; referees: 2 approved]** *F1000Research* 2017, 6(F1000 Faculty Rev):749 (doi: [10.12688/f1000research.11295.1](https://doi.org/10.12688/f1000research.11295.1))

Copyright: © 2017 Ayyaz A *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution Licence](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Grant information: Work from the authors' labs is supported by grants from the Canadian Institutes of Health Research (CIHR) Foundation program, the Terry Fox Research Institute, and the Krembil Foundation to LA and JLW. AA is also supported by a postdoctoral fellow award, part of the University of Toronto's Medicine by Design initiative, which receives funding from the Canada First Research Excellence Fund (CFREF). *The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.*

First published: 26 May 2017, 6(F1000 Faculty Rev):749 (doi: [10.12688/f1000research.11295.1](https://doi.org/10.12688/f1000research.11295.1))

Introduction

Transforming growth factor β (TGF β) signaling pathways have co-evolved with animals¹. Ligands of the TGF β superfamily such as TGF β (1–3), bone morphogenetic proteins (BMPs), activins, nodal, and growth differentiation factors (GDFs) control numerous aspects of animal biology including embryonic development, organogenesis, cell fate decisions, immune modulation, stress responses, and stem cell function^{2–7}. Owing to widespread functional diversity, disruptions in TGF β signaling are also associated with human diseases including cancer, fibrosis, systemic sclerosis, and hereditary disorders^{8–12}. TGF β morphogens often drive contradictory biological outcomes (Figure 1), which has perplexed investigators for decades^{2,9,13–15}. For example, TGF β 1, first described as a transforming growth factor, is also a potent growth inhibitor at benign stages of cancer and promotes metastasis, genetic heterogeneity, and drug resistance in aggressive carcinomas^{8,9,13,14}. Similarly, BMPs also have diverse functions. BMPs prevent self-renewal of the intestinal stem cells (ISCs) by inhibiting Wnt-type MMTV integration site (WNT)/ β -catenin signaling, yet promote specification, expansion, and homing of hematopoietic progenitors^{16–21}. Although multi-layer regulation of TGF β signaling can theoretically explain the dichotomy of activities, the exact molecular contexts that lead to opposite biological output in intact tissues remain elusive. Recent studies utilizing multiple animal and human models have addressed these contradictions and uncovered complex interactions in immune and regenerative tissues that determine specific biological outcomes of TGF β activity. This review will briefly summarize these findings.

TGF β signal transduction

Canonical TGF β Smad signaling is fairly simple^{2,6,22}. Activated ligands, released by the cleavage of their pro-domains in the extracellular matrix, bind to a complex of two type II and type I

transmembrane receptors, inducing type II-mediated phosphorylation of type I receptors at specific serine/threonine residues. This in turn triggers the activation of regulatory Smad (R-Smad) transcription factors, which then complex with the co-transcription factor Smad4 and accumulate in the nucleus, where they alter gene expression^{2,6,22}. Inhibitory Smads (I-Smads), which are themselves induced by TGF β family signaling²³, function in a negative feedback loop to regulate TGF β signaling. The mammalian genome encodes 33 ligands, five type II and seven type I receptors, and eight Smad proteins (including five R-Smads, two I-Smads, and a single co-Smad, Smad4). In *Drosophila*, there are seven ligands, three type II receptors, two type I receptors, two R-Smads (Mad and dSmad2, called Smox), one co-Smad (Medea or Med), and one I-Smad (Dad)^{6,22,24,25}. TGF β signaling is further divided into discrete pathways, as functionally redundant TGF β ligands generally activate a restricted set of corresponding receptors and Smad transcription factors. For example, TGF β (1–3) activate Smad2/3 via TGF β receptors, BMPs stimulate Smad1/5/8 activation via BMP or activin receptors, and activins, inhibins, and GDFs activate activin receptors to phosphorylate Smad2/3^{2,6,22}. However, there are exceptions to this general model, as ligand/receptor promiscuity can lead to crosstalk between these distinct pathways^{26,27}.

TGF β signaling in intestinal repair and colon cancer

Tissue homeostasis is maintained by a rapidly cycling population of LGR5⁺ crypt base columnar ISCs that reside at the bottom of crypts of Lieberkühn²⁸. As ISCs divide asymmetrically, their progeny expands in the transit-amplifying compartment and differentiates into functional lineages as they migrate towards the tips of villi. This baso-apical structural morphology in the mammalian intestine is maintained by two opposing concentration gradients of WNT and BMP signaling pathways²⁹ that sustain the basal regenerative stem/progenitor cell zone and apical

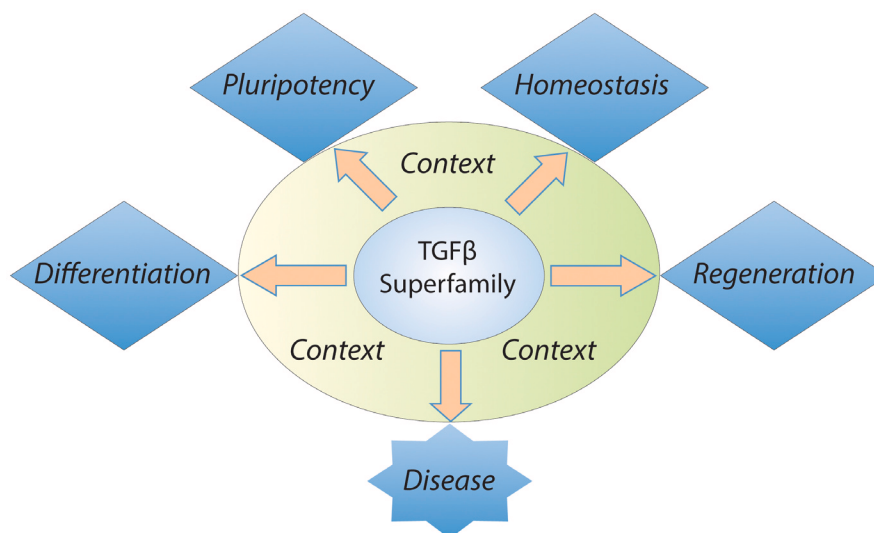


Figure 1. Context-dependent transforming growth factor β (TGF β) superfamily signaling. Diverse biological activities regulated by TGF β pathways are rigorously controlled in a finely calibrated contextual framework. Perturbation in these processes can lead to disease development.

differentiated zone, respectively. Indeed, in humans, inactivating mutations in adenomatous polyposis coli (APC) as well as the BMP receptor 1A (BMPR1A) in ISCs lead to hyperactivate β -catenin function and loss of BMP signaling, respectively, thus enhancing stem cell features and predisposing mutation carriers to cancer development^{30,31}. TGF β also promotes differentiation in the apical regions, and inactivating mutations in core TGF β components are frequently detected in colorectal cancer (CRC). Intriguingly, recent studies propose that the activity of the canonical TGF β pathway is enhanced by the non-canonical WNT ligand Wnt5A during acute injury in the intestine, and this promotes *de novo* generation and fission of crypts that facilitate efficient repair of the intestine^{32,33}. At the molecular level, since the Hippo signaling pathway co-transcription factor yes-associated protein (YAP) is also required for crypt regeneration³⁴, interaction between TGF β and Hippo pathways may explain these observations (see below).

TGF β signaling in immune regulation

The intestinal epithelium is inhabited by trillions of microbes that are kept in check by diverse epithelial and cellular immune responses^{35–37}. The activity of the immune system, however, has to be tightly controlled to prevent inflammatory disorders and maintain homeostatic regeneration of tissues. TGF β signaling is involved in the regulation of these processes^{38–43}. Previously, TGF β signaling was shown to prevent inflammation of the bowel upon activation in the associated dendritic cells⁴⁴. New data shed further light on this process by suggesting that *Clostridium* species within the microbiota induce TGF β 1 expression in colonic dendritic cells in a model of experimental colitis⁴⁵. This in turn stimulates the generation of immunosuppressive regulatory T (Treg) cells, thereby ameliorating the bowel colitis. TGF β 1 also amplifies its own production by activating a Smad3-dependent autocrine signaling loop within dendritic cells, which is, surprisingly, inhibited by Smad2 activity⁴⁵. Although Smad2 regulates TGF β receptor expression in this context, it is not clear what drives the opposing roles of the closely related Smad3 and Smad2.

TGF β signaling was also found to mediate immune-stem cell communication during intestinal repair in *Drosophila*. Macrophages are recruited to the intestinal epithelium upon injury where they secrete the TGF β /BMP homologue Decapentaplegic (Dpp)^{42,46}. Dpp then activates the type II receptor Punt (Put) and type I receptor Saxophone (Sax) complex in the ISCs, which drives nuclear localization of dSmad2, thereby triggering ISC proliferation. This immune regulation of ISC function is required for efficient repair of the damaged intestine and is paramount for survival during pathogen invasion. Interestingly, ISCs can subsequently change their response to Dpp by expressing another type I receptor, Thickveins (Tkv), which, upon activation, phosphorylates the R-Smad Mad to restore stem cell quiescence. Oncogenic transformation of ISCs induced by ectopic expression of epidermal growth factor receptor (EGFR) and Jak/STAT pathways can supersede the growth inhibitory effects of Tkv/Mad signaling and requires chronic dSmad2 activity to promote tumor-like stem cell growth and hyperplasia⁴⁶ (Figure 2). Finally, macrophage-derived Dpp also enhances age-related stem cell dysplasia and epithelial permeability through Sax/dSmad2 signaling^{46,47}. Thus, TGF β signaling has emerged as

an important modulator of immune responses during tissue injury, regeneration, and aging.

TGF β signaling in tumor-associated stroma

TGF β , BMP, and activin signaling play important roles in the crosstalk between tumor cells and the surrounding stroma, although the precise mechanisms are poorly understood^{48,49}. Interestingly, poor prognosis in CRC patients with a stem/serrated/mesenchymal (SSM) subtype was recently linked to the activation of TGF β signaling within cancer-associated fibroblasts (CAFs), which increased the frequency of tumor-initiating cells and the promotion of metastatic invasion in humanized mouse models^{50,51}. Parallel observations were also made in breast cancer patients where both heat shock factor 1 (HSF1) and TGF β signaling activation in CAFs is associated with poor clinical outcome⁵². Another study showed that TGF β signaling induces a mesenchymal transcriptional footprint in genetically engineered intestinal organoid cultures carrying a BRAF^{V600E} mutation⁵³ (Figure 2). Considering the heterogeneous nature of CRC and the paradoxical roles of TGF β in stem cell regulation and CRC progression, continued analyses of interactions between mesenchymal and intestinal tissues under normal and dysplastic conditions are required.

A role for Smad4 in switching TGF β signaling in cancer cells

High TGF β concentrations are associated with drug resistance and poor prognosis in gastrointestinal cancer patients, yet inactivating mutations in core TGF β components are frequently found in these maladies. Indeed, deletion of Smad4 in normal intestinal tissues in combination with mutations in APC, TP53, and Kras lead to the formation of invasive carcinoma in mouse xenografts⁵⁴. Although the immunosuppressive activities of TGF β 1 in the tumor microenvironment have been accepted as one rational explanation, this does not explain the role that TGF β 1 plays within tumor cells lacking functional Smad4 to promote proliferation, metastasis, and apoptotic resistance^{9,13,14}. However, in pancreatic cancer, David *et al.*⁵⁵ have now identified Smad4 as a switch between tumor-suppressive and tumor-promoting activities of TGF β in the tumor cells. Mechanistically, they show that TGF β induces the expression of Sox4 in a Smad4-independent manner that then cooperates with the epithelial lineage determinant Kruppel like factor 5 (Klf5) to promote oncogenic growth in Kras^{G12D}-driven cancers. Restoration of Smad4 activity disrupts Sox4–KLF5 interaction and redirects Sox4 to induce the transcription of pro-apoptotic genes through a lethal epithelial-mesenchymal transition (EMT) program⁵⁵ (Figure 2). Thus, Smad4 functions as a transcriptional switch empowering TGF β 1 to control two different transcriptional programs, each leading to opposite outputs. Interestingly, these findings are in agreement with fly studies where dSmad2 was found to promote tumor-like ISC growth and hyperplasia in a Smad4-independent manner⁴⁶.

Molecular mechanisms underlying contextual TGF β signaling

The Hippo pathway plays a critical role in cell and organ growth and is implicated in tissue regeneration and cancer^{34,56–58}. In the Hippo pathway, a core kinase cassette comprising MST1/2 and LATS1/2 kinases phosphorylate and thereby sequester the related

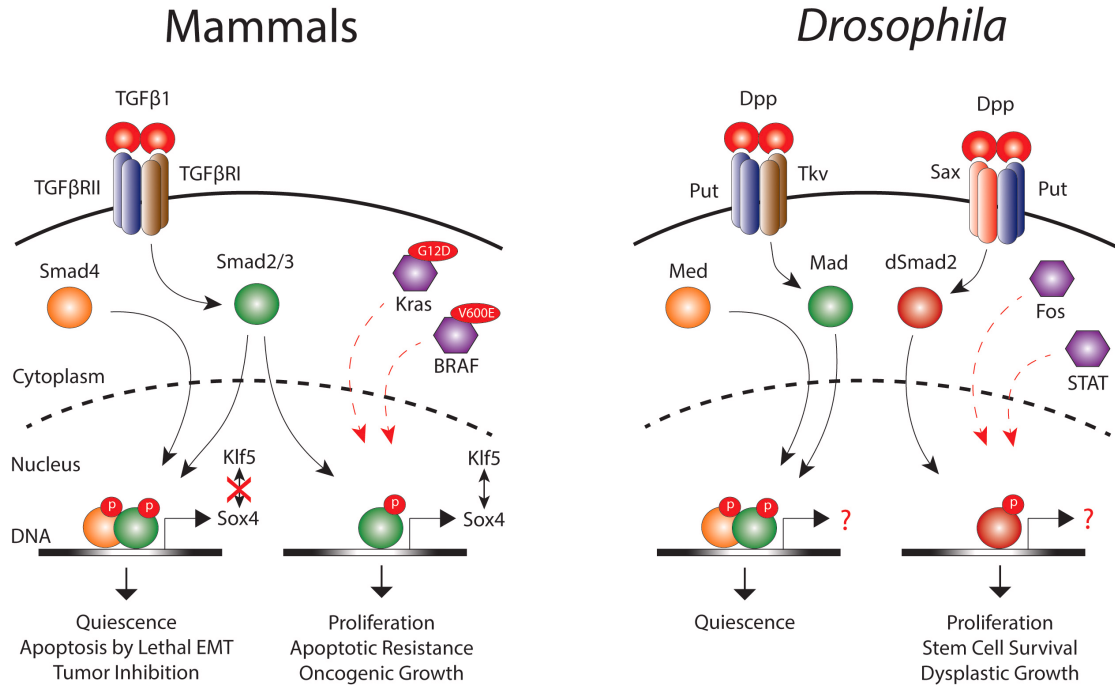


Figure 2. Transforming growth factor β (TGF β) signaling during homeostasis and cancer. In mammals, TGF β 1 activates TGF β receptors to recruit the canonical Smad2/3–Smad4 complex that, upon nuclear translocation, promotes quiescence and induces lethal epithelial-mesenchymal transition (EMT) to limit tumor growth. Loss of Smad4 in Kras^{G12D}-mutant cells as well as acquisition of a BRAF^{V600E} mutation divert the activity of phosphorylated Smad2/3 to promote cell proliferation, survival, and metastatic growth. Similarly, *Drosophila* Decapentaplegic (Dpp) stimulates Punt (Put) and Thickveins (Tkv) receptors to activate the canonical Mad-Med (Smad4 homologue) nuclear complex that promotes quiescence. Overactivation of epidermal growth factor receptor (EGFR)/Fos and Jak/signal transducer and activator of transcription (STAT) signaling re-directs Dpp to activate the alternate Put–Saxophone (Sax) receptor complex. This complex then activates dSmad2, which translocates into the nucleus independently of Med and induces tumor-like stem cell growth and dysplasia.

transcriptional co-activators YAP and transcriptional co-activator with PDZ-binding motif (TAZ) in the cytoplasm, which can also lead to their degradation. Upon inhibition of MST/LATS kinase cassette, YAP/TAZ translocate into the nucleus, where they associate with the DNA-binding partners, such as the TEA domain transcription factors (TEADs), to regulate gene expression. The Hippo pathway is an environmental sensor that responds to a wide range of extrinsic cues that include cell density, cell polarity, metabolic cues, GPCR signaling, and mechanotransduction. The Hippo pathway in turn interacts with several signaling cascades including TGF β , WNT, EGFR/mitogen-associated protein kinase (MAPK), and others to regulate cell proliferation, tissue growth, apoptotic resistance, and tumor progression^{56–58}. In the case of TGF β signaling, when the Hippo pathway is inactive, YAP/TAZ physically interact with the Smad2/3–Smad4 complex to promote its nuclear accumulation, thereby regulating diverse transcriptional programs that maintain pluripotency in embryonic stem cells^{59–61}, regulate differentiation into diverse lineages^{62–67}, enhance wound healing⁶⁸, and promote tumorigenesis in breast cancer, mesothelioma, and hepatocarcinoma models^{69–71}. Recent studies have also uncovered cooperative interactions between YAP and TGF β -regulated Smads that couple mechanotransduction in fibroblasts to TGF β -induced profibrotic gene expression programs

that are important in fibrosis^{72,73}. Interestingly, the TGF β pathway can also regulate Hippo signaling by interacting with the scaffold protein RASSF1A, which is often inactivated in human cancers⁷⁴. Mechanistically, high TGF β activity promotes ubiquitination-based degradation of RASSF1A. This inactivates the MST/LATS kinase cassette, facilitating nuclear localization of the YAP/Smad complex, thereby enhancing the tumorigenic potential of TGF β signaling. Together, these studies indicate that the TGF β and Hippo pathway interactions are finely tuned and disruptions in these processes can alter stem cell function and cell fate decisions and lead to fibrosis and cancer.

TGF β pathway and hematopoiesis in mammals

TGF β pathways control several aspects of blood formation^{21,75}. BMPs have been shown to specify hematopoietic tissues during development and promote heterogeneity by differentially regulating the formation of diverse hematopoietic stem cell (HSC) types that are separately deposited in the fetal liver and bone marrow of developing embryos^{20,21,76}. Moreover, BMPs modulate myeloid lineage specification and promote homing and proliferation of hematopoietic progenitors at postnatal stages^{18,21,77}. TGF β (1–3) ligands, however, are potent inhibitors of hematopoiesis in adults^{21,78}. New studies now identify that megakaryocytes secrete

the bulk of latent TGF β 1 in the bone marrow, which is cleaved by the non-myelinating Schwann cells^{79,80}. Once activated, TGF β 1 stimulates canonical Smad2/3 signaling in multipotent HSCs to promote quiescence. Intriguingly, megakaryocyte-derived TGF β 1 also protects HSCs from exhaustion in a hostile microenvironment, which could be relevant to the development of hematological malignancies⁷⁹. Indeed, leukemia-initiating cells (LICs) in chronic myeloid leukemia (CML) derive therapeutic resistance from active TGF β signaling⁸¹. Although a direct link between megakaryocytes/platelets and the development of hematological malignancies has not been established, platelets are shown to activate TGF β signaling in circulating tumor cells, enhance immune evasion, and facilitate bone metastasis^{82,83}.

BMP signaling in glioma

Gliomas are the most common tumors of the central nervous system^{84,85}. Among these, diffuse intrinsic pontine gliomas (DIPGs) almost exclusively occur in children at the age of 6–8 years. DIPGs exhibit a dismal prognosis with a median survival rate of only 1 year⁸⁶ because no therapeutic treatment is effective against these cancers, primarily owing to their anatomical location. Whole genome exploration studies have identified unique epigenetic changes in DIPG specimens with 78% of patients exhibiting a single amino acid mutation in a histone H3 variant, a lysine replacement to methionine at position 27 (K27M). This histone H3-K27M mutation removes trimethylation from the histone H3 tail, allowing transcriptional derepression that is associated with the induction of stem cell features and cancer development⁸⁷. Intriguingly, four independent studies have now shown that a majority of patients who have the K27M mutation also bear activating mutations in the activin receptor type 1 (ACVR1)^{88–92}. Activity of mutant ACVR1 still requires ligand-mediated activation of type II receptors and does not seem to be tumorigenic alone, since the same ACVR1-activating mutations found in hereditary fibrodysplasia ossificans progressiva (FOP) do not result in cancer predisposition^{93,94}. ACVR1 has not been previously implicated in cancer, thus the link with a mutated histone H3 variant in the context of glioma is particularly intriguing.

Conclusions and perspectives

Extensive efforts in TGF β research have revealed that dynamic interactions between tissues and rapidly changing molecular contexts determine the specific biological output of TGF β signaling in intact tissues. These complex processes are designed to fine-tune cellular reactions and prevent exaggerated responses that may lead to lethal consequences in animals. These interactions also allow TGF β pathways to sense a wide spectrum of constantly changing cellular microenvironments and launch appropriate responses. This complex pattern of tight TGF β regulation also enables just

a few components to control diverse biological activities and creates opportunities for diseased cells to adapt and modify these elements to use for their own growth and survival. Therefore, while it is necessary to keep an open mind when considering such complexities in TGF β signaling, caution must be exercised when using current tools and interpreting specific observations. This is particularly true in pathological tissues where canonical signaling pathways may be altered. In future work, it will be vital to incorporate information about TGF β pathway crosstalk and couple observations of pathway activity to mechanistic molecular and functional assays.

Abbreviations

ACVR1, activin receptor type 1; APC, adenomatous polyposis coli; BMP, bone morphogenetic protein; CAF, cancer-associated fibroblast; CRC, colorectal cancer; DIPG, diffuse intrinsic pontine glioma; Dpp, Decapentaplegic; EGFR, epidermal growth factor receptor; GDF, growth differentiation factors; HSC, hematopoietic stem cell; ISC, intestinal stem cell; I-Smad, inhibitory Smad; K27M, lysine replacement to methionine at position 27; Klf5, Kruppel like factor 5; R-Smad, regulatory Smad; Sax, Saxophone; TAZ, transcriptional co-activator with PDZ-binding motif; TGF β , transforming growth factor beta; Tkv, Thickveins; WNT, Wingless-type MMTV integration site; YAP, yes-associated protein.

Author contributions

All authors contributed to the writing and editing of this article.

Competing interests

The authors declare that they have no competing interests.

Grant information

Work from the authors' labs is supported by grants from the Canadian Institutes of Health Research (CIHR) Foundation program, the Terry Fox Research Institute, and the Krembil Foundation to LA and JLW. AA is also supported by a postdoctoral fellow award, part of the University of Toronto's Medicine by Design initiative, which receives funding from the Canada First Research Excellence Fund (CFREF).

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgements

We thank past and current members of our laboratories for discussions and contributions towards our understanding of signaling pathways.

References

- Huminięcki L, Goldovsky L, Freilich S, *et al.*: **Emergence, development and diversification of the TGF-beta signalling pathway within the animal kingdom.** *BMC Evol Biol.* 2009; **9**: 28. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Massagué J: **TGF β signalling in context.** *Nat Rev Mol Cell Biol.* 2012; **13**(10): 616–30. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Oshimori N, Fuchs E: **The harmonies played by TGF- β in stem cell biology.**



- Cell Stem Cell*. 2012; **11**(6): 751–64.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
4. Mullen AC, Wrana JL: **TGF- β Family Signaling in Embryonic and Somatic Stem-Cell Renewal and Differentiation**. *Cold Spring Harb Perspect Biol*. 2017; pii: a022186.
[PubMed Abstract](#) | [Publisher Full Text](#)
 5. Beyer TA, Narimatsu M, Weiss A, *et al.*: **The TGF β superfamily in stem cell biology and early mammalian embryonic development**. *Biochim Biophys Acta*. 2013; **1830**(2): 2268–79.
[PubMed Abstract](#) | [Publisher Full Text](#)
 6. **F** Morikawa M, Derynck R, Miyazono K: **TGF- β and the TGF- β Family: Context-Dependent Roles in Cell and Tissue Physiology**. *Cold Spring Harb Perspect Biol*. 2016; **8**(5): pii: a021873.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 7. **F** Chen W, Ten Dijke P: **Immunoregulation by members of the TGF β superfamily**. *Nat Rev Immunol*. 2016; **16**(12): 723–40.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 8. Wakefield LM, Hill CS: **Beyond TGF β : roles of other TGF β superfamily members in cancer**. *Nat Rev Cancer*. 2013; **13**(5): 328–41.
[PubMed Abstract](#) | [Publisher Full Text](#)
 9. Bierie B, Moses HL: **Tumour microenvironment: TGFbeta: the molecular Jekyll and Hyde of cancer**. *Nat Rev Cancer*. 2006; **6**(7): 506–20.
[PubMed Abstract](#) | [Publisher Full Text](#)
 10. Piersma B, Bank RA, Boersema M: **Signaling in Fibrosis: TGF- β , WNT, and YAP/TAZ Converge**. *Front Med (Lausanne)*. 2015; **2**: 59.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 11. Lafyatis R: **Transforming growth factor β --at the centre of systemic sclerosis**. *Nat Rev Rheumatol*. 2014; **10**(12): 706–19.
[PubMed Abstract](#) | [Publisher Full Text](#)
 12. McDonald J, Wooderchak-Donahue W, VanSant Webb C, *et al.*: **Hereditary hemorrhagic telangiectasia: genetics and molecular diagnostics in a new era**. *Front Genet*. 2015; **6**: 1.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 13. **F** Akhurst RJ, Padgett RW: **Matters of context guide future research in TGF β superfamily signaling**. *Sci Signal*. 2015; **8**(399): re10.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 14. **F** Zhang Q, Yu N, Lee C: **Mysteries of TGF- β Paradox in Benign and Malignant Cells**. *Front Oncol*. 2014; **4**: 94.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 15. Akhurst RJ: **The paradoxical TGF- β vasculopathies**. *Nat Genet*. 2012; **44**(8): 838–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 16. Bhatia M, Bonnet D, Wu D, *et al.*: **Bone morphogenetic proteins regulate the developmental program of human hematopoietic stem cells**. *J Exp Med*. 1999; **189**(7): 1139–48.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 17. He XC, Zhang J, Tong WG, *et al.*: **BMP signaling inhibits intestinal stem cell self-renewal through suppression of Wnt-beta-catenin signaling**. *Nat Genet*. 2004; **36**(10): 1117–21.
[PubMed Abstract](#) | [Publisher Full Text](#)
 18. Khurana S, Buckley S, Schouteden S, *et al.*: **A novel role of BMP4 in adult hematopoietic stem and progenitor cell homing via Smad independent regulation of integrin- $\alpha 4$ expression**. *Blood*. 2013; **121**(5): 781–90.
[PubMed Abstract](#) | [Publisher Full Text](#)
 19. Khurana S, Melacarne A, Yadak R, *et al.*: **SMAD signaling regulates CXCL12 expression in the bone marrow niche, affecting homing and mobilization of hematopoietic progenitors**. *Stem Cells*. 2014; **32**(11): 3012–22.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 20. **F** Crisan M, Solaimani Kartalaei P, Neagu A, *et al.*: **BMP and Hedgehog Regulate Distinct AGM Hematopoietic Stem Cells Ex Vivo**. *Stem Cell Reports*. 2016; **6**(3): 383–95.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 21. **F** Blank U, Karlsson S: **TGF- β signaling in the control of hematopoietic stem cells**. *Blood*. 2015; **125**(23): 3542–50.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 22. Weiss A, Attisano L: **The TGFbeta superfamily signaling pathway**. *Wiley Interdiscip Rev Dev Biol*. 2013; **2**(1): 47–63.
[PubMed Abstract](#) | [Publisher Full Text](#)
 23. Nakao A, Afrakhte M, Morán A, *et al.*: **Identification of Smad7, a TGFbeta-inducible antagonist of TGF-beta signalling**. *Nature*. 1997; **389**(6651): 631–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
 24. Parker L, Stathakis DG, Arora K: **Regulation of BMP and activin signaling in *Drosophila***. *Prog Mol Subcell Biol*. 2004; **34**: 73–101.
[PubMed Abstract](#) | [Publisher Full Text](#)
 25. Upadhyay A, Moss-Taylor L, Kim MJ, *et al.*: **TGF- β Family Signaling in *Drosophila***. *Cold Spring Harb Perspect Biol*. 2017; pii: a022152.
[PubMed Abstract](#) | [Publisher Full Text](#)
 26. Daly AC, Randall RA, Hill CS: **Transforming growth factor beta-induced Smad1/5 phosphorylation in epithelial cells is mediated by novel receptor complexes and is essential for anchorage-independent growth**. *Mol Cell Biol*. 2008; **28**(22): 6889–902.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 27. Grönroos E, Kingston LJ, Ramachandran A, *et al.*: **Transforming growth factor β inhibits bone morphogenetic protein-induced transcription through novel phosphorylated Smad1/5-Smad3 complexes**. *Mol Cell Biol*. 2012; **32**(14): 2904–16.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 28. Beumer J, Clevers H: **Regulation and plasticity of intestinal stem cells during homeostasis and regeneration**. *Development*. 2016; **143**(20): 3639–49.
[PubMed Abstract](#) | [Publisher Full Text](#)
 29. Crosnier C, Stamatakis D, Lewis J: **Organizing cell renewal in the intestine: stem cells, signals and combinatorial control**. *Nat Rev Genet*. 2006; **7**(5): 349–59.
[PubMed Abstract](#) | [Publisher Full Text](#)
 30. **F** Qi Z, Li Y, Zhao B, *et al.*: **BMP restricts stemness of intestinal Lgr5+ stem cells by directly suppressing their signature genes**. *Nat Commun*. 2017; **8**: 13824.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 31. **F** Barker N, Ridgway RA, van Es JH, *et al.*: **Crypt stem cells as the cells-of-origin of intestinal cancer**. *Nature*. 2009; **457**(7449): 608–11.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 32. **F** Miyoshi H, Ajima R, Luo CT, *et al.*: **Wnt5a potentiates TGF- β signaling to promote colonic crypt regeneration after tissue injury**. *Science*. 2012; **338**(6103): 108–13.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 33. **F** Fischer JM, Calabrese PP, Miller AJ, *et al.*: **Single cell lineage tracing reveals a role for Tgfr2 in intestinal stem cell dynamics and differentiation**. *Proc Natl Acad Sci U S A*. 2016; **113**(43): 12192–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 34. Hong AW, Meng Z, Guan KL: **The Hippo pathway in intestinal regeneration and disease**. *Nat Rev Gastroenterol Hepatol*. 2016; **13**(6): 324–37.
[PubMed Abstract](#) | [Publisher Full Text](#)
 35. Perez-Lopez A, Behnsen J, Nuccio SP, *et al.*: **Mucosal immunity to pathogenic intestinal bacteria**. *Nat Rev Immunol*. 2016; **16**(3): 135–48.
[PubMed Abstract](#) | [Publisher Full Text](#)
 36. Mowat AM, Bain CC: **Mucosal macrophages in intestinal homeostasis and inflammation**. *J Innate Immun*. 2011; **3**(6): 550–64.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 37. Coombes JL, Powrie F: **Dendritic cells in intestinal immune regulation**. *Nat Rev Immunol*. 2008; **8**(6): 435–46.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 38. Neurath MF: **Cytokines in inflammatory bowel disease**. *Nat Rev Immunol*. 2014; **14**(5): 329–42.
[PubMed Abstract](#) | [Publisher Full Text](#)
 39. **F** Karin M, Clevers H: **Reparative inflammation takes charge of tissue regeneration**. *Nature*. 2016; **529**(7586): 307–15.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 40. **F** Xavier RJ, Podolsky DK: **Unravelling the pathogenesis of inflammatory bowel disease**. *Nature*. 2007; **448**(7152): 427–34.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 41. **F** Biancheri P, Giuffrida P, Docena GH, *et al.*: **The role of transforming growth factor (TGF)- β in modulating the immune response and fibrogenesis in the gut**. *Cytokine Growth Factor Rev*. 2014; **25**(1): 45–55.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 42. Weaver LN, Drummond-Barbosa D: **Gut healing: haemocytes aid via Sax and Tkv jazes it down**. *Nat Cell Biol*. 2015; **17**(6): 707–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
 43. **F** Pull SL, Doherty JM, Mills JC, *et al.*: **Activated macrophages are an adaptive element of the colonic epithelial progenitor niche necessary for regenerative responses to injury**. *Proc Natl Acad Sci U S A*. 2005; **102**(1): 99–104.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 44. **F** Travis MA, Reizis B, Melton AC, *et al.*: **Loss of integrin alpha(v)beta8 on dendritic cells causes autoimmunity and colitis in mice**. *Nature*. 2007; **449**(7160): 361–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 45. **F** Kashiwagi I, Morita R, Schichita T, *et al.*: **Smad2 and Smad3 Inversely Regulate TGF- β Autoinduction in *Clostridium butyricum*-Activated Dendritic Cells**. *Immunity*. 2015; **43**(1): 65–79.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 46. Ayyaz A, Li H, Jasper H: **Haemocytes control stem cell activity in the *Drosophila* intestine**. *Nat Cell Biol*. 2015; **17**(6): 736–48.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 47. **F** Tian A, Jiang J: **Intestinal epithelium-derived BMP controls stem cell self-renewal in *Drosophila* adult midgut**. *eLife*. 2014; **3**: e01857.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 48. Pickup MW, Owens P, Moses HL: **TGF- β , Bone Morphogenetic Protein, and Activin Signaling and the Tumor Microenvironment**. *Cold Spring Harb Perspect Biol*. 2017; **9**(5): pii: a022285.
[PubMed Abstract](#) | [Publisher Full Text](#)
 49. Costanza B, Umelo IA, Bellier J, *et al.*: **Stromal Modulators of TGF- β in Cancer**. *J Clin Med*. 2017; **6**(1): pii: E7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

50. **F** Isella C, Terrasi A, Bellomo SE, *et al.*: **Stromal contribution to the colorectal cancer transcriptome.** *Nat Genet.* 2015; 47(4): 312–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
51. **F** Calon A, Lonardo E, Berenguer-Llargo A, *et al.*: **Stromal gene expression defines poor-prognosis subtypes in colorectal cancer.** *Nat Genet.* 2015; 47(4): 320–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
52. **F** Scherz-Shouval R, Santagata S, Mendillo ML, *et al.*: **The reprogramming of tumor stroma by HSF1 is a potent enabler of malignancy.** *Cell.* 2014; 158(3): 564–78.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
53. **F** Fessler E, Drost J, van Hooff SR, *et al.*: **TGF β signaling directs serrated adenomas to the mesenchymal colorectal cancer subtype.** *EMBO Mol Med.* 2016; 8(7): 745–60.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
54. **F** Drost J, van Jaarsveld RH, Ponsioen B, *et al.*: **Sequential cancer mutations in cultured human intestinal stem cells.** *Nature.* 2015; 521(7550): 43–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
55. **F** David CJ, Huang YH, Chen M, *et al.*: **TGF- β Tumor Suppression through a Lethal EMT.** *Cell.* 2016; 164(5): 1015–30.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
56. Zanonato F, Cordenonsi M, Piccolo S: **YAP/TAZ at the Roots of Cancer.** *Cancer Cell.* 2016; 29(6): 783–803.
[PubMed Abstract](#) | [Publisher Full Text](#)
57. Moroiishi T, Hansen CG, Guan KL: **The emerging roles of YAP and TAZ in cancer.** *Nat Rev Cancer.* 2015; 15(2): 73–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
58. Attisano L, Wrana JL: **Signal integration in TGF- β , WNT, and Hippo pathways.** *F1000Prime Rep.* 2013; 5: 17.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
59. Varelas X, Sakuma R, Samavarchi-Tehrani P, *et al.*: **TAZ controls Smad nucleocytoplasmic shuttling and regulates human embryonic stem-cell self-renewal.** *Nat Cell Biol.* 2008; 10(7): 837–48.
[PubMed Abstract](#) | [Publisher Full Text](#)
60. **F** Varelas X, Samavarchi-Tehrani P, Narimatsu M, *et al.*: **The Crumbs complex couples cell density sensing to Hippo-dependent control of the TGF- β -SMAD pathway.** *Dev Cell.* 2010; 19(6): 831–44.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
61. Beyer TA, Weiss A, Khomchuk Y, *et al.*: **Switch enhancers interpret TGF- β and Hippo signaling to control cell fate in human embryonic stem cells.** *Cell Rep.* 2013; 5(6): 1611–24.
[PubMed Abstract](#) | [Publisher Full Text](#)
62. **F** Mahoney JE, Mori M, Szymaniak AD, *et al.*: **The hippo pathway effector Yap controls patterning and differentiation of airway epithelial progenitors.** *Dev Cell.* 2014; 30(2): 137–50.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
63. **F** Sun Y, Yong KM, Villa-Diaz LG, *et al.*: **Hippo/YAP-mediated rigidity-dependent motor neuron differentiation of human pluripotent stem cells.** *Nat Mater.* 2014; 13(6): 599–604.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
64. Yang JY, Cho SW, An JH, *et al.*: **Osteoblast-targeted overexpression of TAZ increases bone mass in vivo.** *PLoS One.* 2013; 8(2): e56585.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
65. Zhang H, von Gise A, Liu Q, *et al.*: **Yap1 is required for endothelial to mesenchymal transition of the atrioventricular cushion.** *J Biol Chem.* 2014; 289(27): 18681–92.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
66. Narimatsu M, Samavarchi-Tehrani P, Varelas X, *et al.*: **Distinct polarity cues direct Taz/Yap and TGF β receptor localization to differentially control TGF β -induced Smad signaling.** *Dev Cell.* 2015; 32(5): 652–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
67. Yao M, Wang Y, Zhang P, *et al.*: **BMP2-SMAD signaling represses the proliferation of embryonic neural stem cells through YAP.** *J Neurosci.* 2014; 34(36): 12039–48.
[PubMed Abstract](#) | [Publisher Full Text](#)
68. Lee M, Ran Byun M, Furutani-Seiki M, *et al.*: **YAP and TAZ regulate skin wound healing.** *J Invest Dermatol.* 2014; 134(2): 518–25.
[PubMed Abstract](#) | [Publisher Full Text](#)
69. Hiemer SE, Szymaniak AD, Varelas X: **The transcriptional regulators TAZ and YAP direct transforming growth factor β -induced tumorigenic phenotypes in breast cancer cells.** *J Biol Chem.* 2014; 289(19): 13461–74.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
70. Fujii M, Toyoda T, Nakanishi H, *et al.*: **TGF- β synergizes with defects in the Hippo pathway to stimulate human malignant mesothelioma growth.** *J Exp Med.* 2012; 209(3): 479–94.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
71. **F** Nishio M, Sugimachi K, Goto H, *et al.*: **Dysregulated YAP1/TAZ and TGF- β signaling mediate hepatocarcinogenesis in *Mob1a/1b*-deficient mice.** *Proc Natl Acad Sci U S A.* 2016; 113(1): E71–80.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
72. Szeto SG, Narimatsu M, Lu M, *et al.*: **YAP/TAZ Are Mechanoregulators of TGF- β -Smad Signaling and Renal Fibrogenesis.** *J Am Soc Nephrol.* 2016; 27: 3117–28.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
73. **F** Liu F, Lagares D, Choi KM, *et al.*: **Mechanosignaling through YAP and TAZ drives fibroblast activation and fibrosis.** *Am J Physiol Lung Cell Mol Physiol.* 2015; 308(4): L344–57.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
74. **F** Pefani DE, Pankova D, Abraham AG, *et al.*: **TGF- β Targets the Hippo Pathway Scaffold RASSF1A to Facilitate YAP/SMAD2 Nuclear Translocation.** *Mol Cell.* 2016; 63(1): 156–66.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
75. Cichon MA, Radisky DC: **Cutting the brakes and flooring the gas: how TMEPAI turns TGF- β into a tumor promoter.** *Genes Cancer.* 2014; 5(9–10): 303–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
76. **F** Crisan M, Kartalaei PS, Vink CS, *et al.*: **BMP signalling differentially regulates distinct haematopoietic stem cell types.** *Nat Commun.* 2015; 6: 8040.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
77. **F** Cook BD, Evans T: **BMP signaling balances murine myeloid potential through SMAD-independent p38MAPK and NOTCH pathways.** *Blood.* 2014; 124(3): 393–402.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
78. Zhou L, Nguyen AN, Sohail D, *et al.*: **Inhibition of the TGF-beta receptor I kinase promotes hematopoiesis in MDS.** *Blood.* 2008; 112(8): 3434–43.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
79. **F** Zhao M, Perry JM, Marshall H, *et al.*: **Megakaryocytes maintain homeostatic quiescence and promote post-injury regeneration of hematopoietic stem cells.** *Nat Med.* 2014; 20(11): 1321–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
80. **F** Yamazaki S, Ema H, Karlsson G, *et al.*: **Nonmyelinating Schwann cells maintain hematopoietic stem cell hibernation in the bone marrow niche.** *Cell.* 2011; 147(5): 1146–58.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
81. **F** Naka K, Hoshii T, Muraguchi T, *et al.*: **TGF-beta-FOXO signalling maintains leukaemia-initiating cells in chronic myeloid leukaemia.** *Nature.* 2010; 463(7281): 676–80.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
82. **F** Leblanc R, Peyruchaud O: **Metastasis: new functional implications of platelets and megakaryocytes.** *Blood.* 2016; 128(1): 24–31.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
83. **F** Labelle M, Begum S, Hynes RO: **Direct signaling between platelets and cancer cells induces an epithelial-mesenchymal-like transition and promotes metastasis.** *Cancer Cell.* 2011; 20(5): 576–90.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
84. Khuong-Quang DA, Buczkowicz P, Rakopoulos P, *et al.*: **K27M mutation in histone H3.3 defines clinically and biologically distinct subgroups of pediatric diffuse intrinsic pontine gliomas.** *Acta Neuropathol.* 2012; 124(3): 439–47.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
85. Weller M, Wick W, Aldape K, *et al.*: **Glioma.** *Nat Rev Dis Primers.* 2015; 1: 15017.
[PubMed Abstract](#) | [Publisher Full Text](#)
86. Jones C, Baker SJ: **Unique genetic and epigenetic mechanisms driving paediatric diffuse high-grade glioma.** *Nat Rev Cancer.* 2014; 14(10): 651–661.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
87. Li M, Liu GH, Izpisua Belmonte JC: **Navigating the epigenetic landscape of pluripotent stem cells.** *Nat Rev Mol Cell Biol.* 2012; 13(8): 524–35.
[PubMed Abstract](#) | [Publisher Full Text](#)
88. **F** Taylor KR, Mackay A, Truffaux N, *et al.*: **Recurrent activating *ACVR1* mutations in diffuse intrinsic pontine glioma.** *Nat Genet.* 2014; 46(5): 457–61.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
89. **F** Buczkowicz P, Hoeman C, Rakopoulos P, *et al.*: **Genomic analysis of diffuse intrinsic pontine gliomas identifies three molecular subgroups and recurrent activating *ACVR1* mutations.** *Nat Genet.* 2014; 46(5): 451–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
90. **F** Fontebasso AM, Papillon-Cavanagh S, Schwartzentruber J, *et al.*: **Recurrent somatic mutations in *ACVR1* in pediatric midline high-grade astrocytoma.** *Nat Genet.* 2014; 46(5): 462–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
91. Zadeh G, Aldape K: ***ACVR1* mutations and the genomic landscape of pediatric diffuse glioma.** *Nat Genet.* 2014; 46(5): 421–2.
[PubMed Abstract](#) | [Publisher Full Text](#)
92. Villanueva MT: **Genetics: *ACVR1* mutations—a key piece in paediatric diffuse glioma.** *Nat Rev Clin Oncol.* 2014; 11(6): 300.
[PubMed Abstract](#) | [Publisher Full Text](#)
93. Bagarova J, Vonner AJ, Armstrong KA, *et al.*: **Constitutively active ALK2 receptor mutants require type II receptor cooperation.** *Mol Cell Biol.* 2013; 33(12): 2413–24.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
94. Shore EM, Kaplan FS: **Inherited human diseases of heterotopic bone formation.** *Nat Rev Rheumatol.* 2010; 6(9): 518–27.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Open Peer Review

Current Referee Status:  

Editorial Note on the Review Process

F1000 Faculty Reviews are commissioned from members of the prestigious F1000 Faculty and are edited as a service to readers. In order to make these reviews as comprehensive and accessible as possible, the referees provide input before publication and only the final, revised version is published. The referees who approved the final version are listed with their names and affiliations but without their reports on earlier versions (any comments will already have been addressed in the published version).

The referees who approved this article are:

Version 1

- 1 **Peter ten Dijke**, Leiden University Medical Center, Leiden, Netherlands
Competing Interests: No competing interests were disclosed.
- 1 **Harold L Moses**, Vanderbilt-Ingram Cancer Center, Nashville, Nashville, TN, USA
Competing Interests: No competing interests were disclosed.