

COMMENTARY

BUB1-bling over with Possibilities

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Abstract

In a new report, Nyati et al. identified a previously undetected participant mediating both canonical signaling, i.e., TGF- β receptor kinase mediated, and non-canonical signaling, budding uninhibited by benzimidazole 1 (BUB1).

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Despite more than a quarter century and a vast literature, understanding transforming growth factor- β (TGF β) signaling continues to be a major research enterprise because TGF β is a central hub in both homeostasis and disease. The TGF β 1 isoform is the founding member of a superfamily that orchestrates cell interactions, regulates phenotype, and acts as a critical switch in many key tissue repair processes. In a new report, Nyati et al. has identified a previously undetected participant mediating both canonical, i.e., TGF β receptor kinase mediated, and non-canonical signaling [1]. This group conducted a small interfering RNA (siRNA) screen of the human kinome using a live-cell reporter for TGF β receptor (TGFBR) activity in two cancer lines. The screen successfully identified many proteins with known roles, and the authors chose to characterize budding uninhibited by benzimidazole 1 (BUB1) as a target using a high stringency strategy for selection. BUB1 was validated in six malignant and non-malignant human cell lines from various tissues in which siRNA activity abrogated the activation of SMAD2 and SMAD3 as well as components of the non-canonical signaling cascade (c-JUN, p38 mitogen-activated protein kinase, and AKT). Although BUB1 knockdown in one cell line, A549, also decreased TGFBR type I (TGFBR1), this was not necessary in other

cell lines nor did BUB1 siRNA mimic TGFBR1 small molecule inhibitor effects, confirming it as an independent mediator of TGF β signaling.

BUB1 depletion abrogated the formation of the TGFBR1–TGFBR2 type II (TGFBR2) complex. The authors showed that BUB1 promotes the TGFBR1–TGFBR2 complex formation, in which BUB1 interacts with both TGFBR1 and TGFBR2, but does not require TGFBR1 kinase activity. However, BUB1 kinase activity is necessary for TGF β canonical signaling even though BUB1 does not directly phosphorylate TGFBR1 or phosphorylate purified SMAD3 *in vitro*. Importantly, BUB1 kinase activity is also important for non-canonical signaling through Akt and p38 mitogen-activated protein kinase. The authors conclude that BUB1 forms a ternary complex with the ligand and both receptors; signaling requires BUB1's Ser/Thr kinase activity, but the actual BUB1 substrate required for TGF β signaling is as yet unknown.

Thus, BUB1 joins the ongoing delineation of TGF β signaling in a complex network that controls its actions across cell types, but this new member is particularly intriguing in regards to cancer. The TGF β switch from tumor suppressor to tumor promoter remains one of the major hallmarks of epithelial cancers, whose normal counterparts are profoundly growth inhibited by femtomolar TGF β concentrations. BUB1 is a mitotic checkpoint protein that also has a role in regulating kinetochore-microtubule attachments (reviewed in [2]). Notably, its deletion rapidly leads to aneuploidy, which is a relatively underappreciated consequence of TGF β 1 knockout [3,4].

Nyati et al. have uncovered a pathway interaction that has far-reaching implications in understanding the loss of genomic stability in cancer and may have therapeutic applications as well. Intriguingly, there is growing evidence that TGF β is necessary for genomic stability and pluripotency in stem cells and DNA damage response in differentiated cells. In one study of five human embryonic stem cell lines, BUB1 is among the 1% of genes expressed across all lines in the undifferentiated states, and clustered with previously reported stemness genes responsible for self-renewal and pluripotent differentiation, concurrent with highly expressed TGF β

Abbreviations: TGF β , transforming growth factor- β ; BUB1, budding uninhibited by benzimidazole 1; TGFBR2, TGF β receptor type II; TGFBR1, TGF β receptor type I
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signaling components, TGFBR1 and SMAD2 [5]. Of particular interest is that either BUB1 [6] or TGF β 1 deletion [7] impairs DNA damage recognition and increases sensitivity to ionizing radiation. This is one example of many neoplastic processes in which TGF β is implicated, and underscores how the addition of BUB1 as a necessary component of TGF β signaling has the potential to clarify the aspects of TGF β phenotypes that have long puzzled the community.

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