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IGF2 as a Proposed Indirect Rheostat of TGF-β-Driven Intravasation: A Liebig-Like Model of TGFBR1 Regulation

Alimukhammed Samatuly
aliplaneta1@gmail.com

ABSTRACT

Metastatic breast cancer cells can disseminate through collective or single-cell modes, and transient TGF-β signaling has been shown to promote a single-cell motility program associated with blood-borne dissemination. This narrative review evaluates a hypothesis in which insulin-like growth factor 2 (IGF2) indirectly tunes the competence of this TGF-β-driven program by influencing the availability and RNA-regulatory activity of IGF2BP3, thereby affecting TGFBR1 expression. A structured literature search of PubMed/MEDLINE and Google Scholar was conducted through October 5, 2026, with emphasis on peer-reviewed mechanistic studies of TGF-β receptor abundance, circTGFBR2(3-6), IGF2BP3, IGF2 signaling, and cancer-cell motility. Direct evidence supports three separate modules: (i) the lower-abundance TGF-β receptor can constrain SMAD signaling; (ii) circTGFBR2(3-6) scaffolds IGF2BP3 and m6A-modified TGFBR1 mRNA in breast-cancer models, increasing TGFBR1 mRNA stability and TGF-β/SMAD signaling; and (iii) mTORC2-dependent phosphorylation of the homologous IGF2BP family proteins IMP1/IGF2BP1 and IMP3/IGF2BP3 has been demonstrated in separate experimental systems. These findings do not directly establish that IGF2 levels alter the circTGFBR2(3-6)-IGF2BP3-TGFBR1 complex or shift the rate-limiting component of this axis. We therefore present the IGF2 rheostat as a hypothesis-generating model: IGF2-rich signaling states may increase functionally available IGF2BP3, potentially raising the TGFBR1 signaling ceiling until another component, such as circTGFBR2(3-6), becomes limiting. The model yields testable predictions but requires direct validation in a common breast-cancer system.

INTRODUCTION

Cancer intravasation - the entry of tumor cells into the vasculature - is a major bottleneck in metastasis because only cells that cross the endothelial barrier can enter the circulation and potentially seed distant organs. Tumor cells may disseminate individually or as multicellular clusters, and these modes differ in their survival, plasticity, and metastatic behavior [1,2]. The mode of invasion and vascular entry is therefore not merely a geometric feature of a tumor; it reflects dynamic signaling states within cancer cells and their microenvironment.

Transforming growth factor beta (TGF-β) signaling is one pathway that can alter this behavior. Giampieri et al. used intravital imaging of breast-cancer dissemination to show that TGF-β signaling is transiently and locally activated in motile single cells. Blocking TGF-β signaling prevented single-cell motility in vivo while preserving collective movement, whereas constitutive signaling promoted single-cell motility and intravasation [3]. These observations establish a direct link between TGF-β pathway activity and a single-cell motility program, but they do not identify all upstream determinants of how strongly an individual tumor cell can respond to TGF-β.

One determinant is receptor abundance. Li et al. combined mathematical modeling with experiments across cancer cell lines and single cells and found that TGF-β/SMAD output follows a Liebig-like "law of the minimum": when TGFBR1 and TGFBR2 are imbalanced, the lower-abundance receptor has the stronger influence on downstream SMAD activity [4]. This principle suggests that mechanisms that alter the abundance of the currently limiting receptor can change the signaling ceiling without changing ligand concentration.

A recently described post-transcriptional mechanism provides a route by which TGFBR1 abundance can be altered. Wang et al. identified circTGFBR2(3-6), a circular RNA derived from TGFBR2 pre-mRNA, as an assembly platform for IGF2BP3 and TGFBR1 mRNA in breast-cancer models. The complex stabilizes TGFBR1 mRNA in an m6A-dependent manner and potentiates TGF-β/SMAD signaling, epithelial plasticity, and migration [6]. Separately, IGF2 is a growth factor frequently reactivated in cancer that signals through IGF1R and insulin receptor isoform A (IR-A), engaging growth and survival pathways that include PI3K-associated signaling networks [5]. IGF2BP3 itself is an oncofetal RNA-binding protein whose function can be modulated by phosphorylation and by competition among target RNAs [10,11].

This review asks whether these experimentally separate observations can be integrated into a testable model in which IGF2 acts as an indirect rheostat of TGF-β pathway competence rather than as a direct switch for intravasation. The central proposal is deliberately narrower than a claim of an established pathway: IGF2 signaling may influence the functional availability of IGF2BP3, which could alter post-transcriptional stabilization of TGFBR1 and thereby tune the maximum TGF-β/SMAD response. The complete causal sequence has not been directly demonstrated and is treated throughout this review as a hypothesis requiring experimental validation.

METHODS

Literature search strategy

For this revision, a structured narrative literature search was conducted on October 5, 2026 using PubMed/MEDLINE and Google Scholar. Search combinations included: ("TGF-beta" OR "TGFβ") AND (TGFBR1 OR TGFBR2) AND (receptor abundance OR SMAD2 OR Liebig); (circTGFBR2 OR "circTGFBR2(3-6)") AND IGF2BP3 AND TGFBR1; (IGF2BP3 OR IMP3) AND (Ser183 OR phosphorylation OR mTORC2); IGF2 AND (IGF1R OR IR-A) AND cancer; and TGF-β AND (single-cell motility OR intravasation) AND breast cancer. Reference lists of key primary studies and mechanistic reviews were also screened to identify foundational work.

Eligible sources were peer-reviewed English-language primary studies that directly tested at least one mechanistic link relevant to the proposed model, together with authoritative reviews used for pathway-level context. Priority was given to primary experimental evidence when a causal statement was made. Preprints, non-peer-reviewed sources, studies lacking a relevant molecular or phenotypic endpoint, and papers whose findings could not be connected to the proposed pathway were excluded. No formal meta-analysis was performed because the included studies addressed different molecular links, experimental systems, and outcome measures. The review should therefore be considered a structured narrative synthesis rather than a systematic review.

Evidence classification and figure preparation

To avoid conflating evidence across experimental systems, relationships directly tested within a cited study are described as experimentally supported, whereas cross-study connections are labeled proposed, inferred, predicted, or hypothetical. In Figures 1-3, solid arrows denote experimentally supported relationships and dashed arrows denote inferred relationships that have not been tested as an integrated pathway. Figures 1-3 are original schematics created by the author using GPAI-assisted illustration; no published figure was directly reproduced. Scientific content, labels, and evidence classification were manually reviewed and revised by the author.

TGF-B SIGNALING AND RECEPTOR-ABUNDANCE LIMITATION

In canonical signaling, TGF-β ligand promotes formation of a receptor complex containing TGFBR2 and TGFBR1. TGFBR2 activates TGFBR1, which phosphorylates SMAD2 and SMAD3; these receptor-regulated SMADs associate with SMAD4, accumulate in the nucleus, and regulate transcriptional programs involved in proliferation, differentiation, migration, and epithelial plasticity [7-9].

The relevance of this pathway to dissemination was demonstrated directly in breast-cancer models by Giampieri et al. [3]. Intravital imaging revealed both collective and single-cell motility, with TGF-β reporter activity enriched transiently in motile single cells. TGF-β pathway inhibition blocked single-cell movement but did not abolish collective invasion. Importantly, cells restricted to collective invasion retained lymphatic dissemination but lost efficient blood-borne metastasis, while constitutive TGF-β signaling increased single-cell motility and intravasation [3]. These data support TGF-β as a regulator of motility state rather than a universal determinant of all forms of invasion.

Li et al. addressed a different mechanistic level: how receptor abundance shapes TGF-β/SMAD output [4]. Their modeling and experiments showed that when TGFBR1 and TGFBR2 are present at unequal levels, signaling becomes particularly sensitive to changes in the receptor that is less abundant. Thus, TGFBR1 is not inherently the limiting receptor; TGFBR2 can become limiting in another cellular context. This context dependence is central to the model developed here because an increase in TGFBR1 can only raise the signaling ceiling when TGFBR1 is the limiting component.

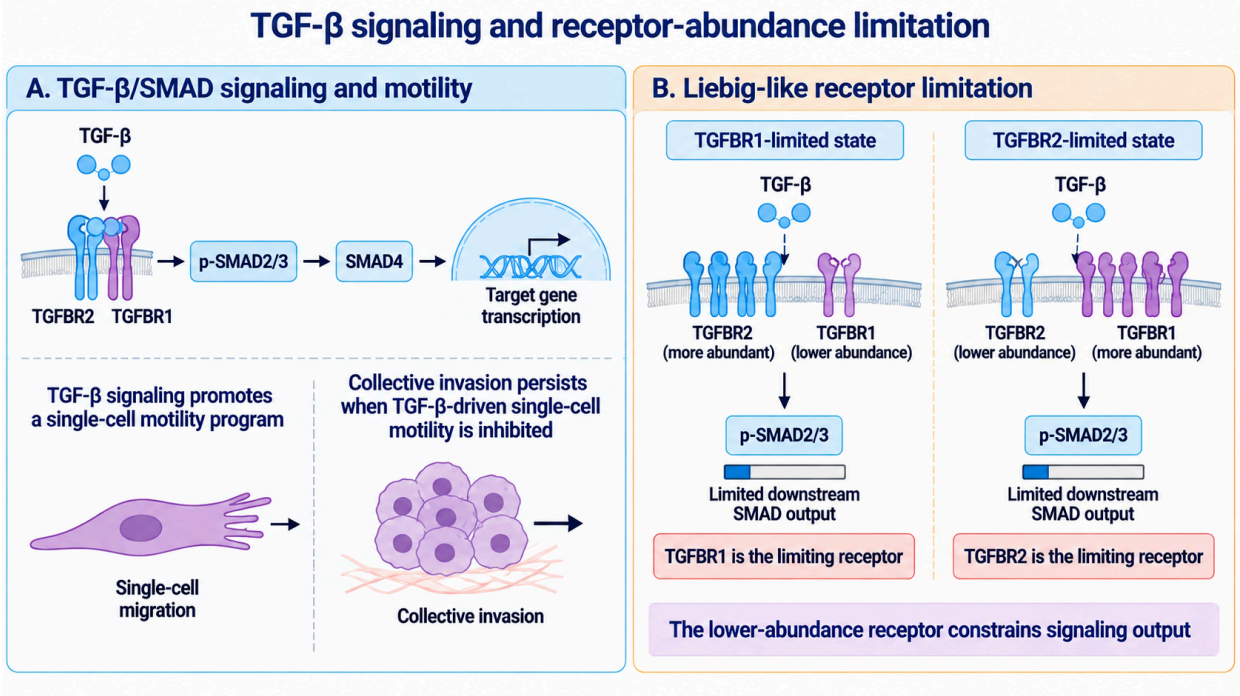

Figure 1. TGF-β signaling and receptor-abundance limitation. (A) Canonical TGF-β signaling proceeds through TGFBR2/TGFBR1, SMAD2/3 phosphorylation, SMAD4, and target-gene transcription. Breast-cancer models show that TGF-β signaling promotes a single-cell motility program, whereas collective invasion can persist when TGF-β-driven single-cell motility is inhibited [3]. (B) Under a Liebig-like limiting-factor framework, the lower-abundance receptor - TGFBR1 or TGFBR2 - constrains downstream SMAD signaling [4]. Original schematic created by the author using GPAI-assisted illustration; scientific content was manually reviewed. Based on concepts from Giampieri et al. [3] and Li et al. [4].

CIRCTGFBR2(3-6)-IGF2BP3 REGULATION OF TGFBR1 EXPRESSION

Wang et al. identified circTGFBR2(3-6), generated by back-splicing of TGFBR2 pre-mRNA exons 3-6, as a post-transcriptional enhancer of TGF-β signaling in breast-cancer models [6]. Much of the mechanistic work was performed in MDA-MB-231 cells, with complementary experiments in MCF10A-M2 cells and additional breast-cancer lines. Across a panel of breast-cancer cell lines, circTGFBR2(3-6) showed a trend toward higher expression in aggressive basal-type than luminal-type cells, supporting - but not proving - relevance to basal-like and triple-negative disease contexts [6].

Mechanistically, circTGFBR2(3-6) facilitates association of IGF2BP3 with TGFBR1 mRNA. Wang et al. showed that TGFBR1 mRNA stability decreases when circTGFBR2(3-6) is depleted and increases when the circRNA is overexpressed. IGF2BP3 is required for this effect, and the interaction with TGFBR1 mRNA depends on m6A modification within the TGFBR1 transcript [6]. The resulting increase in TGFBR1 expression potentiates TGF-β-induced SMAD2 phosphorylation, epithelial-mesenchymal plasticity, and migration. These relationships are experimentally supported within the breast-cancer system and are therefore treated as the established post-transcriptional module of the model.

The phenotypic evidence must nevertheless be described precisely. The Wang et al. study directly measured TGF-β signaling, EMT-related responses, migration, and in vivo extravasation of MDA-MB-231 cells in zebrafish [6]. It did not directly test whether this axis determines intravasation from a primary breast tumor or whether it controls the choice between collective and single-cell intravasation. Those steps remain extrapolations from the separate TGF-β motility evidence of Giampieri et al. [3].

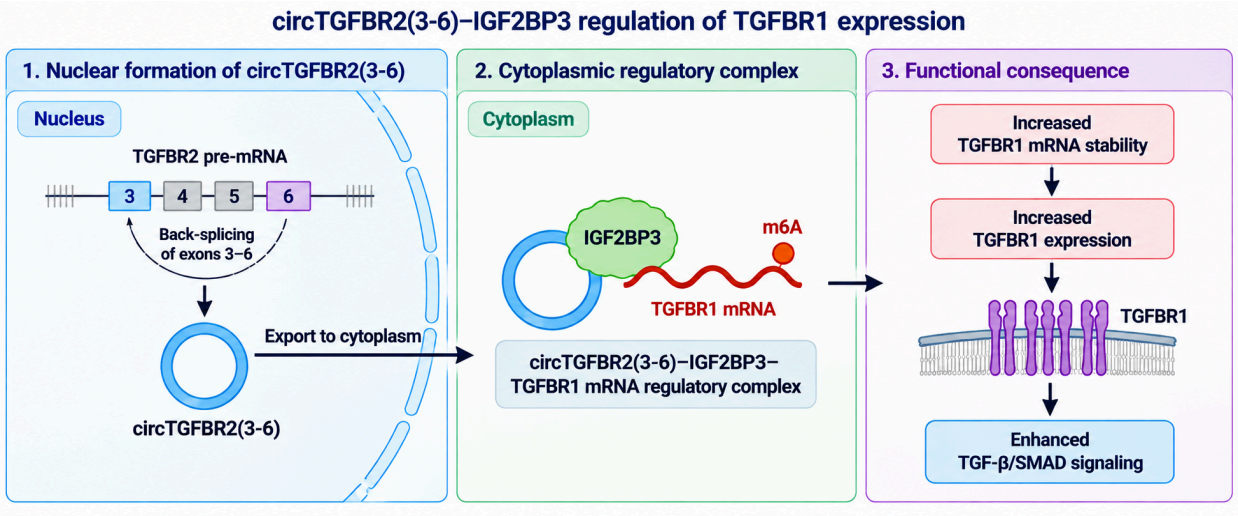

Figure 2. Experimentally supported circTGFBR2(3-6)-IGF2BP3 regulation of TGFBR1 expression. Back-splicing of TGFBR2 pre-mRNA generates circTGFBR2(3-6), which participates in a cytoplasmic regulatory complex with IGF2BP3 and m6A-modified TGFBR1 mRNA. This complex stabilizes TGFBR1 mRNA, increases TGFBR1 expression, and potentiates TGF-β/SMAD signaling [6]. The proposed IGF2-dependent coupling is intentionally not shown in this figure. Original schematic created by the author using GPAI-assisted illustration; scientific content was manually reviewed. Based on Wang et al. [6].

IGF SIGNALING AND IGF2BP3 PHOSPHORYLATION: EVIDENCE FROM SEPARATE SYSTEMS

IGF2 is frequently reactivated in malignancy and can signal through IGF1R and IR-A, stimulating pathways that support proliferation, survival, metabolic adaptation, and metastatic behavior [5]. IR-A is especially relevant because it binds IGF2 with relatively high affinity and is often enriched in cancer. These observations establish IGF2 as a plausible upstream modulator of signaling state, but they do not demonstrate that IGF2 changes the circTGFBR2(3-6)-IGF2BP3-TGFBR1 complex in breast-cancer cells.

A separate body of work shows that IGF2BP-family proteins can be regulated by mTOR-dependent phosphorylation. Dai et al. identified phosphorylation of IMP3/IGF2BP3 at Ser183 in human RD rhabdomyosarcoma cells and established mTORC2-dependent cotranslational phosphorylation of the homologous IMP1/IGF2BP1 at Ser181, with functional consequences for IGF2 RNA binding and translation in mouse embryonic fibroblasts [11]. Reviews of IGF2BP3 biology have therefore proposed phosphorylation as one mechanism that can modify target-RNA regulation [10]. However, the strongest

functional evidence in the Dai study focused on IMP1, and neither Dai et al. nor Wang et al. showed that IGF2 stimulation in breast-cancer cells increases IGF2BP3 Ser183 phosphorylation or that Ser183 phosphorylation enhances binding to TGFBR1 mRNA. Those connections are therefore treated as inferred rather than established.

EXPERIMENTAL CONTEXT AND BOUNDARIES OF INTEGRATION

The proposed model integrates studies performed at different biological scales and in different experimental systems. Giampieri et al. directly linked TGF-β activity to single-cell motility and intravasation in breast-cancer dissemination models [3]. Li et al. established the receptor-abundance principle using mathematical models, cancer cell lines, and single-cell measurements of SMAD signaling [4], but did not test intravasation. Wang et al. established the circTGFBR2(3-6)-IGF2BP3-TGFBR1 mechanism mainly in MDA-MB-231 and MCF10A-M2 systems and tested extravasation in zebrafish [6], but did not manipulate IGF2 levels or IGF2BP3 Ser183 phosphorylation. Dai et al. identified IGF2BP3 Ser183 phosphorylation in RD rhabdomyosarcoma cells and carried out the principal functional phosphorylation experiments with IMP1 in mouse embryonic fibroblasts [11]. Belfiore et al. summarize IGF2 receptor signaling across multiple cancer contexts rather than within the same breast-cancer model [5].

These differences do not invalidate cross-study hypothesis generation, but they set the evidentiary boundary. The integrated pathway should not be described as a demonstrated TNBC mechanism until the relevant links are tested in the same breast-cancer system. In particular, the model requires direct evidence that changing IGF2 signaling alters the functionally available IGF2BP3 pool, changes assembly or occupancy of the circTGFBR2(3-6)-IGF2BP3-TGFBR1 complex, modifies TGFBR1 mRNA stability or receptor abundance, and ultimately changes TGF-β-dependent motility or intravasation.

PROPOSED IGF2 RHEOSTAT MODEL

The model proposed here treats IGF2 as a rheostat rather than an on/off motility switch. Its starting point is the experimentally supported observation that TGF-β pathway output can be limited by receptor abundance [4] and that circTGFBR2(3-6)/IGF2BP3 can raise TGFBR1 expression [6]. The additional hypothesis is that the functional availability of IGF2BP3 is itself tunable by signaling state. Because IGF receptor signaling engages PI3K-associated networks and mTORC2 can phosphorylate IGF2BP-family proteins in separate systems [5,10,11], an IGF2-rich state could plausibly be associated with a larger pool of RNA-regulatory-competent IGF2BP3. This specific coupling has not yet been demonstrated in breast cancer.

In the lower-IGF2 state of the model, functional IGF2BP3 availability is predicted to be relatively limiting. Under that condition, even if circTGFBR2(3-6) is present, formation or productive engagement of the regulatory complex may remain constrained, leaving TGFBR1 mRNA less stable and the TGFBR1 signaling ceiling lower. In a higher-IGF2 state, the model predicts greater functional availability of IGF2BP3 and greater engagement of the circTGFBR2(3-6)-IGF2BP3-TGFBR1 module. If TGFBR1 is initially the limiting TGF-β receptor, increased TGFBR1 expression could raise the SMAD signaling

ceiling. Once IGF2BP3 is no longer limiting, another component - potentially circTGFBR2(3-6), TGFBR2, ligand, or competing RNA targets - could become the dominant constraint. Thus, the predicted shift from IGF2BP3 limitation to circTGFBR2(3-6) limitation is a testable model output, not an experimentally established transition.

Target competition is an important complication. IGF2BP3 binds many RNAs, including oncogenic transcripts and IGF2-related targets [10]. Increasing the functional IGF2BP3 pool would therefore not necessarily channel that protein specifically toward TGFBR1 mRNA. The amount of circTGFBR2(3-6), the m6A state of TGFBR1 mRNA, relative abundance of competing transcripts, subcellular localization, and other post-translational modifications could all determine whether the proposed rheostat operates in a given cell.

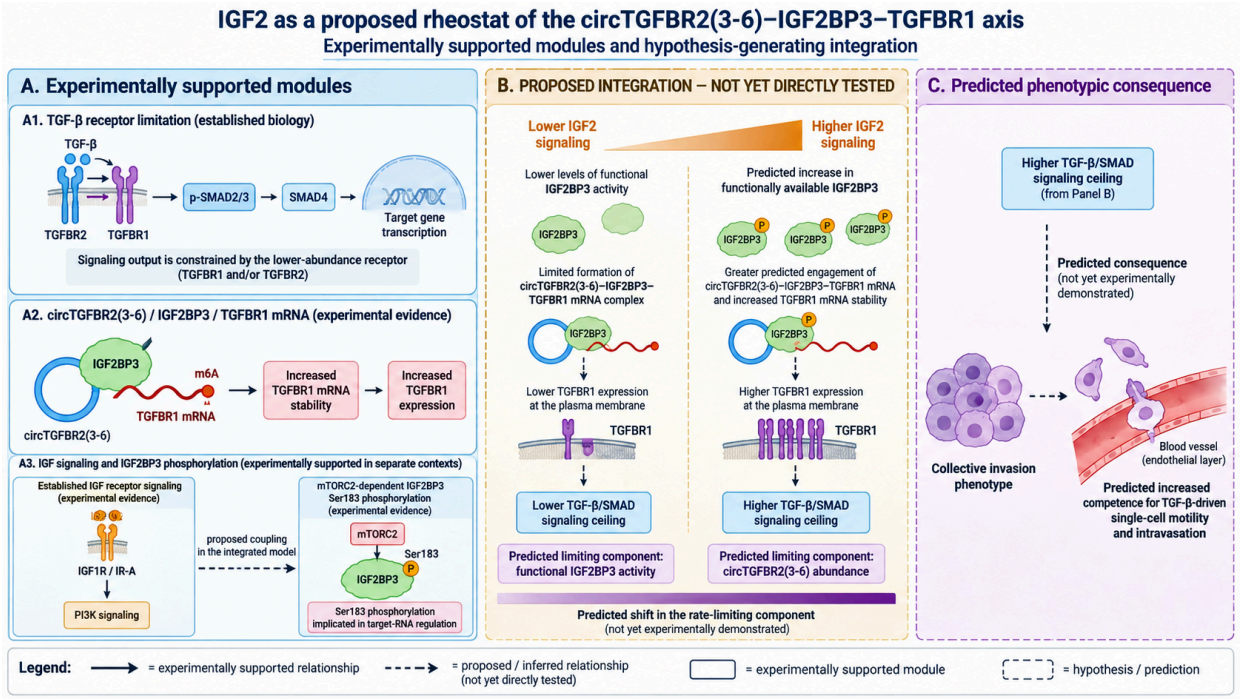

Figure 3. Proposed integration of IGF signaling with the circTGFBR2(3-6)-IGF2BP3-TGFBR1 axis. Panel A summarizes experimentally supported modules established in separate contexts. Panel B presents the hypothesis-generating integration proposed in this review: differences in IGF2 signaling state may alter functional IGF2BP3 availability and thereby influence engagement of the circTGFBR2(3-6)-IGF2BP3-TGFBR1 regulatory complex, potentially changing the rate-limiting component of the system. Panel C illustrates the predicted phenotypic consequence of a higher TGF-β/SMAD signaling ceiling. Solid arrows denote experimentally supported relationships; dashed arrows denote proposed or inferred relationships that have not been directly tested as an integrated pathway. Original schematic created by the author using GPAI-assisted illustration; scientific content was manually reviewed. Based on concepts reported in Giampieri et al. [3], Li et al. [4], Wang et al. [6], Mancarella and Scotlandi [10], and Dai et al. [11].

TESTABLE PREDICTIONS AND IMPLICATIONS

The model can be evaluated experimentally with a relatively direct series of perturbations. First, IGF2 levels or IGF1R/IR-A signaling should be manipulated in the same breast-cancer cell line in which circTGFBR2(3-6), IGF2BP3, and TGFBR1 are measured. IGF2BP3 Ser183 phosphorylation should then be quantified directly rather than inferred from pathway activity. RNA immunoprecipitation or related occupancy assays can test whether changes in signaling alter IGF2BP3 association with circTGFBR2(3-6) and TGFBR1 mRNA. Actinomycin-D chase experiments can determine TGFBR1 mRNA half-life, while receptor abundance and p-SMAD2/3 can report the downstream signaling consequence.

Second, epistasis experiments can distinguish correlation from causality. For example, an IGF2-dependent effect on TGFBR1 should be lost when circTGFBR2(3-6) or IGF2BP3 is depleted if the proposed route is correct. Conversely, forced restoration of TGFBR1 expression should rescue downstream TGF-β signaling even when the post-transcriptional module is disrupted. Phosphorylation-site mutants of IGF2BP3 could test whether Ser183 is required for any effect of the signaling state on TGFBR1 regulation. Finally, intravital or orthotopic breast-cancer models would be required to determine whether these molecular changes actually alter single-cell versus collective intravasation rather than only migration or extravasation.

Clinical implications should therefore remain provisional. The circTGFBR2(3-6)-IGF2BP3-TGFBR1 module may eventually contribute to a biomarker panel for tumors with high TGF-β pathway competence, and the model may help explain context-dependent responses to therapies that target IGF or TGF-β signaling. However, no biomarker or therapeutic claim follows directly from the present synthesis. Validation across patient-derived breast-cancer models, especially basal-like and triple-negative tumors, would be required before translational use can be justified.

LIMITATIONS

This review has several limitations. It is a structured narrative review rather than a systematic review or meta-analysis, and the evidence base is intentionally mechanistic rather than exhaustive. The central hypothesis is assembled from studies that differ in species, cell type, tumor model, and experimental endpoint. The proposed role of IGF2 in altering IGF2BP3 functional availability has not been demonstrated in the circTGFBR2(3-6)/TGFBR1 breast-cancer system. Likewise, Wang et al. measured migration and extravasation rather than primary-tumor intravasation, whereas Giampieri et al. established the intravasation phenotype in a separate experimental framework. These limitations are not peripheral to the model; they define the experiments required to validate or falsify it.

CONCLUSION

Evidence from separate studies supports three mechanistic observations: TGF-β signaling can promote a single-cell motility program associated with intravasation; the lower-abundance TGF-β receptor can constrain SMAD signaling output; and circTGFBR2(3-6)/IGF2BP3 can stabilize TGFBR1 mRNA and potentiate TGF-β signaling in breast-cancer models [3,4,6]. Separately, IGF2 is a major cancer-associated

growth factor, and IGF2BP-family proteins can be regulated by mTOR-dependent phosphorylation [5,10,11].

The novel contribution of this review is not the claim that these observations already form one validated pathway. Rather, it is the proposal that they may form a context-dependent regulatory circuit in which IGF2-associated signaling tunes the functional availability of IGF2BP3 and thereby changes the TGFBR1 signaling ceiling. If this coupling exists, the identity of the rate-limiting component could shift as signaling state changes, producing rheostat-like rather than binary control. Direct perturbation of IGF2, IGF2BP3 phosphorylation, complex formation, TGFBR1 stability, and intravasation within the same breast-cancer model will be required to determine whether this framework is correct.

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ABOUT THE AUTHOR

Alimukhammed Samatuly is a student at Bilim-Innovation Specialized Boarding School for Gifted Boys in Astana, Kazakhstan. A national biology olympiad gold medalist, whose research on the structural basis of IGF2 selectivity for IR-A spans molecular oncology and computational biology. His broader interests include quantum biology and AI/ML applications in biomedical research.

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