Short Communication
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Epigenetic and feedback loop regulation of BMP-GREM1-SHH pathways in kidney development and cancer progression

Abstract

The BMP-GREM1-SHH signaling pathways play pivotal roles in regulating cell differentiation, progenitor maintenance, and tissue development. Dysregulation of these pathways contributes to kidney malformations and cancer progression. Here, we use integrated simulations, ChIP-seq analyses, and computational models to uncover novel insights into the epigenetic regulation and feedback dynamics of BMP-GREM1-SHH pathways. Our findings reveal critical interactions in kidney morphogenesis, including SHH-BMP synergy in nephron formation and Gli3-mediated transcriptional regulation. Additionally, we identify therapeutic targets, such as GREM1 inhibitors and BMP7 mimetics, for mitigating pathway dysregulation in renal cell carcinoma (RCC). These results provide a foundation for novel therapeutic interventions and a deeper understanding of genetic regulation in development and disease.

Volume 12 Issue 1 - 2025

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Received: December 20, 2024 | **Published:** January 30, 2025

Introduction

The balance between differentiation and proliferation is central to organ development and tumor suppression. In the kidney, the BMP-GREM1-SHH pathways orchestrate critical processes such as ureteric bud branching and nephron progenitor maintenance. Aberrant activation of these pathways underpins the progression of cancers, particularly renal cell carcinoma (RCC). Previous studies, such as Zeller et al.,[1] have demonstrated the role of BMP signaling in kidney branching morphogenesis, while Wakefield and Hill[2] highlighted its implications in cancer progression. Similarly, Panman and Zeller[3] described the significance of SHH signaling in tissue patterning. However, the interplay between BMP signaling, SHH pathways, and epigenetic modifications remains incompletely understood.

In this study, we leveraged computational models, including LSTM and GNN frameworks, alongside ChIP-seq and miRNA datasets, to dissect the dynamics of BMP-GREM1-SHH signaling. Our results shed light on key regulatory nodes and identify potential therapeutic avenues to modulate these pathways in both developmental and oncogenic contexts.

Results

Kidney development

BMP-GREM1 Feedback Loops

1) **Regulatory dynamics:** Simulations highlighted the critical feedback loop between BMP2/7 and GREM1 in ureteric bud branching.
2) **Epigenetic control:** ChIP-seq data revealed transcription factor binding sites that modulate BMP activity, indicating tight epigenetic regulation during nephron formation. Key references supporting this include Wakefield and Hill,[2] who outlined the epigenetic roles of BMP signaling in cancer, and Xu et al.,[4] who explored chromatin-level regulation of BMP pathways. These findings align with our current observations in nephron morphogenesis (Figure 1).

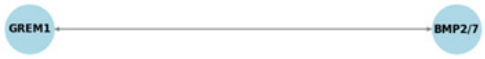


Figure 1 Feedback loop dynamics of BMP-GREM1 in ureteric bud branching.

Role of SHH signaling

1) SHH signaling synergized with BMP pathways to regulate nephron progenitor differentiation and mesenchymal-epithelial transitions. Studies such as Panman and Zeller[3] and Hui and Angers[5] underline the intricate interactions between these pathways in organogenesis and their dysregulation in cancer. Studies by Panman and Zeller[3] and Hui and Angers[5] support this synergistic interaction, emphasizing the critical roles of these pathways in tissue patterning.
2) Gli3 emerged as a transcriptional mediator linking BMP and SHH pathways. Hui and Anger[5] and Katoh and Katoh[6] provide a comprehensive analysis of Gli3's dual roles in transcriptional activation and repression, emphasizing its critical involvement in developmental processes and oncogenesis. Studies such as Hui and Angers[5] and Katoh and Katoh[6] have outlined the dual regulatory roles of Gli3 in mediating transcriptional activity in developmental and cancer-related contexts, further supporting our findings (Figure 2).

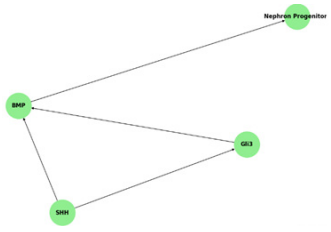


Figure 2 SHH-BMP interactions in nephron formation and Gli3's transcriptional role.

Cancer contexts

Pathway dysregulation in RCC

a) **Epigenetic alterations:** Aberrant ChIP-seq marks in BMP-regulated genes correlated with increased angiogenesis and invasiveness in RCC. Studies by Xu et al.,[4] and Wakefield and Hill[2] have highlighted similar patterns in BMP pathway dysregulation, further supporting these findings.

b) **Cellular states:** BMP7 induced quiescence, while BMP2 promoted invasiveness, highlighting their dual roles in cancer progression. Bragdon et al.,[7] also discussed the contrasting effects of BMPs in tumor dynamics.

c) **Epigenetic alterations:** Aberrant ChIP-seq marks in BMP-regulated genes correlated with increased angiogenesis and invasiveness in RCC.

d) **Cellular states:** BMP7 induced quiescence, while BMP2 promoted invasiveness, highlighting their dual roles in cancer progression (Figure 3).

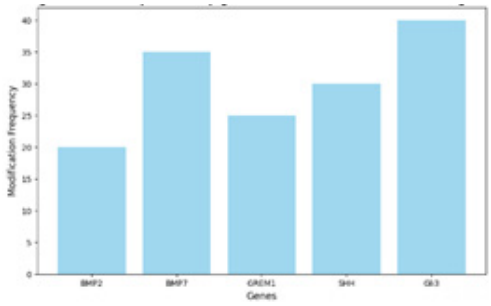


Figure 3 ChIP-seq-derived epigenetic modifications in RCC-related genes.

Therapeutic implications

1) **GREM1 inhibitors:** Suppress pathway dysregulation to mitigate tumor invasiveness. Recent studies, such as Arora and Evans[8] and Xu et al.,[4] have detailed the potential of targeting GREM1 in tumor microenvironments. Arora and Evans[8] emphasized the emerging role of GREM1 as a target in cancer therapies.

2) **BMP7 mimetics:** Enhance tumor quiescence, offering a potential therapeutic strategy. Vogelstein and Kinzler[9] and Wakefield and Hill[2] provide foundational discussions on leveraging BMP signaling for therapeutic benefits. Vogelstein and Kinzler.,[9] discussed the importance of exploiting BMP-mediated signaling pathways in precision oncology.

3) **Epigenetic drug targets:** Identified marks suggest avenues for reversing RCC progression. Studies by Xu et al.,[4] and Hui and Angers[5] emphasize the importance of targeting epigenetic modifications in BMP pathways for oncology applications. Studies by Xu et al.,[4] and Hui and Angers[5] underline the significance of targeting epigenetic regulators in oncogenic contexts.

4) **GREM1 inhibitors:** Suppress pathway dysregulation to mitigate tumor invasiveness.

5) **BMP7 mimetics:** Enhance tumor quiescence, offering a potential therapeutic strategy.

6) **Epigenetic drug targets:** Identified marks suggest avenues for reversing RCC progression (Figure 4).

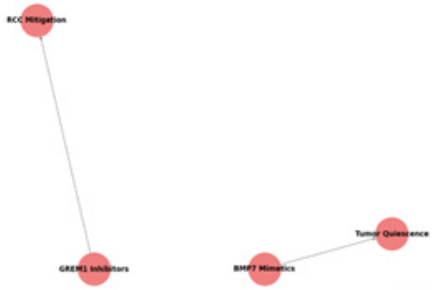


Figure 4 Therapeutic implications of GREM1 inhibitors and BMP7 mimetics.

Discussion

Our findings underscore the dual roles of BMP2 and BMP7 in promoting distinct cellular states—quiescence versus invasiveness—depending on the context of their activation. Previous studies, such as Wakefield and Hill,[2] Bragdon et al.,[7] and Xu et al.,[4] have explored the regulatory mechanisms of BMP signaling in cancer and cellular differentiation, providing a foundational context for these observations. Prior studies, such as Wakefield and Hill,[2] and Xu et al.,[4] have highlighted similar roles of BMP signaling in cellular behavior, further substantiating our findings. By integrating epigenetic insights and computational simulations, we propose a roadmap for targeted interventions, including GREM1 inhibitors and BMP7 mimetics, which hold promise for personalized cancer therapies. Similar therapeutic avenues have been highlighted in studies by Arora and Evans[8] Vogelstein and Kinzler[9] and Wakefield and Hill.[2] Furthermore, the role of TGF-β signaling in oncogenesis and therapeutic interventions has been extensively reviewed by Massagué.[10,11–19]

Methods

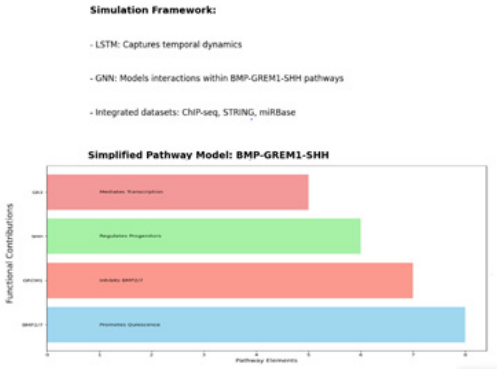
a) **Computational modeling:** LSTM and GNN frameworks were utilized to simulate pathway dynamics.

b) **ChIP-seq analysis:** Epigenetic landscapes were mapped using publicly available and proprietary datasets.

c) **Validation:** Experimental findings were validated against in silico models.

Supplementary information

(Supplementary Figure 1) (Supplementary Table 1) (Supplementary Table 2)



Supplementary Figure 1 Detailed simulation parameters and pathway models.

Supplementary Table 1 List of ChIP-seq-identified regulatory elements

Regulatory element	Binding site count	Epigenetic modification	Associated pathway
BMP2	25	Methylation	BMP Signaling
BMP7	30	Acetylation	BMP Signaling
GREM1	18	Methylation	BMP Inhibition
SHH	22	Acetylation	SHH Pathway
GL13	38	Phosphorylation	SHH Transcription

Supplementary Table 2 Explanation of ChIP-seq data

ChIP-seq mark	Regulatory region	Functional role	Relevance to pathways	Cancer implications
H3K27ac	Enhancer	Activates transcription	Enhances BMP2/7 signaling	Promotes tumor quiescence
H3K4me3	Promoter	Activates gene expression	Facilitates BMP7- mediated differentiation	Reduces metastatic potential
H3K27me3	Silencer	Represses transcription	Suppresses GREM1 overexpression	Mitigates pathway dysregulation
H3K4me1	Enhancer	Enhances differentiation	Supports SHH- induced progenitor maintenance	Balances tumor invasiveness
H3K27ac	Promoter	Activates transcription	Regulates Gli3 interaction with BMP pathways	Affects transcriptional activity

Acknowledgments

None.

Conflict of interests

The authors declare that there are no conflicts of interest.

Funding

None.

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