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Editorial

The Pathogenic Potential of RUNX2

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Runx2 is a well-known transcription factor for bone development. The current understanding of the other aspects of Runx2 functions is at an early stage. The roles of Runx2 in nonosseous tissues are gradually discovered. Of interest, Xiao *et al*. showed the value of Runx2 as a novel prognostic biomarker and as a potential therapeutic target for lung cancer through bioinformatic analysis.[1] This is an interesting and valuable study.

Lung cancer is one of the most common malignancies, which leads to substantial mortality globally.[2] Xiao *et al*. explored the expression levels, functions, and prognostic values of Runx2 in lung cancer via bioinformatics analysis.[1] Bioinformatics is predominantly a discipline that handles genetic information.[3,4] Easy access to bioinformatics tools and the efficient analyses of bioinformatics data are of vital importance to integrate distributed studies and to establish new hypotheses. The contribution of the internet to this integration is significant. Some limitations in the study of Xiao *et al*. should be mentioned.[1] First, more analysis of the online data on Runx2 in lung cancer, which excludes confounders, such as age, tumor stage, and recurrence status should be refined. In addition, large scale experiments and multicenter clinical trials are required to confirm the role of Runx2 in lung cancer.

Studies have reported that Runx2 could participate in disorders of bone metabolism, ectopic calcification of the cardiovascular system, the abnormal development of teeth, tumorigenesis, and organ fibrosis. Osteoblast's proliferation and differentiation are probably regulated by Runx2. Sun *et al*. defined the functional role of VSMC-derived Runx2 in regulating vascular calcification and promoting infiltration of macrophages into calcified lesions to form osteoclast-like cells.[5] Elevated Runx2 could transcriptionally activate genes mediating tumor progression and metastasis, which includes the Runx2 target gene osteopontin (*OPN*). Studies had shown that Runx2 control *OPN* levels.[6] In addition, the Runx2/*OPN* axis could regulate the ability of osteosarcoma cells to attach to pulmonary endothelial cells as a key step in the metastasis of osteosarcoma cells to the lung.[6] The detailed information on Runx2 in the regulation of pathogenicity are summarized in Table 1.[7–25]

Of interest, some factors could influence the expression of Runx2, which include: (1) microRNAs. The deletion of the microRNA processing enzyme Dicer leads to decreased expression of miRNAs and Runx2, which suggests a critical role for microRNA in the regulation of Runx2. A regulatory effect of Runx2-related microRNAs in the skeleton has been described, such as miR-23a, miR-30a, miR-449a, and miR-22.[26] The biogenesis and activity of microRNAs are under sophisticated control at transcriptional and post-transcriptional levels, which restricts miRNA expression to particular tissues or developmental stages; (2) some traditional Chinese medicines have been reported to influence the expression of Runx2.[27,28] Icariin, a flavonoid isolated from the herb Epimedium pubescens, could induce osteogenic differentiation *in vitro* in a Runx2-dependent manner;[29] and (3) the changes in the internal environment. Hyperglycemia, hyperphosphate, and oxidative stress could affect the expression of Runx2.[30–32] A better understanding of the regulation mechanism of Runx2 contributed to the development of target drugs. The factors that affect Runx2 expression should be studied further.

The term bioinformatics has been established for two decades. With the advancement of bioinformatics concepts, data can be accessed and collected on a global scale. As discussed previously, the role of Runx2 as a transcription factor in skeletal system, ectopic calcification, abnormal development of teeth, tumorigenesis, and organ fibrosis has attracted the attention or researchers (Fig. 1). The mechanism of how Runx2 could regulate these diseases requires further research. Strategies that target Runx2 could be potentials for the treatment of related diseases.

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Abbreviations: ECM, extracellular matrix; OPN, osteopontin; VSMC, vascular smooth muscle cell.

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Table 1. Effects and mechanism of Runx2 in multiple systems

Target sites	Effects	Mechanisms	References
Bone	Promote bone formation	1. Enhance the proliferation of osteoblast progenitors 2. Enhance the proliferation of suture mesenchymal cells and induce their commitment into osteoblast lineage cells	7–10
Cardiovascular	Induce vascular and aortic valve calcification	1. VSMC-derived Runx2 promote the calfication of VSMC and formation of vascular osteoclasts 2. Promotes osteoblasts differentiation of human aortic valve interstitial cells	5,11
Teeth	Tooth formation and eruption	1. Form calcified tooth tissue 2. Regulate proliferation of the dental lamina 3. Regulates the alveolar remodeling process	12–14
Tumorigenesis	Osteosarcoma, none-small cell lung cancer, breast cancer, prostate cancer, and renal cell carcinomas	1. Regulate epithelial-mesenchymal transition 2. Affects tumor microenvironment remodeling 3. Regulates tumor growth, invasion, and metastasis	6,15–20
Organ fibrosis	1. Aortic fibrosis 2. Renal fibrosis 3. Pulmonary fibrosis 4. Myocardial fibrosis	1. Increased TGF-beta signaling pathway 2. Increased ECM expression 3. Contributes to profibrotic cell function	21–25

VSMC, vascular smooth muscle cell; ECM, extracellular matrix.

Conflict of interest

The authors have no conflict of interest related to this publication.

Author contributions

Yuan Cheng conceived and designed this study. Ni Lihua and Yuan Cheng wrote the manuscript and approved the submitted version.

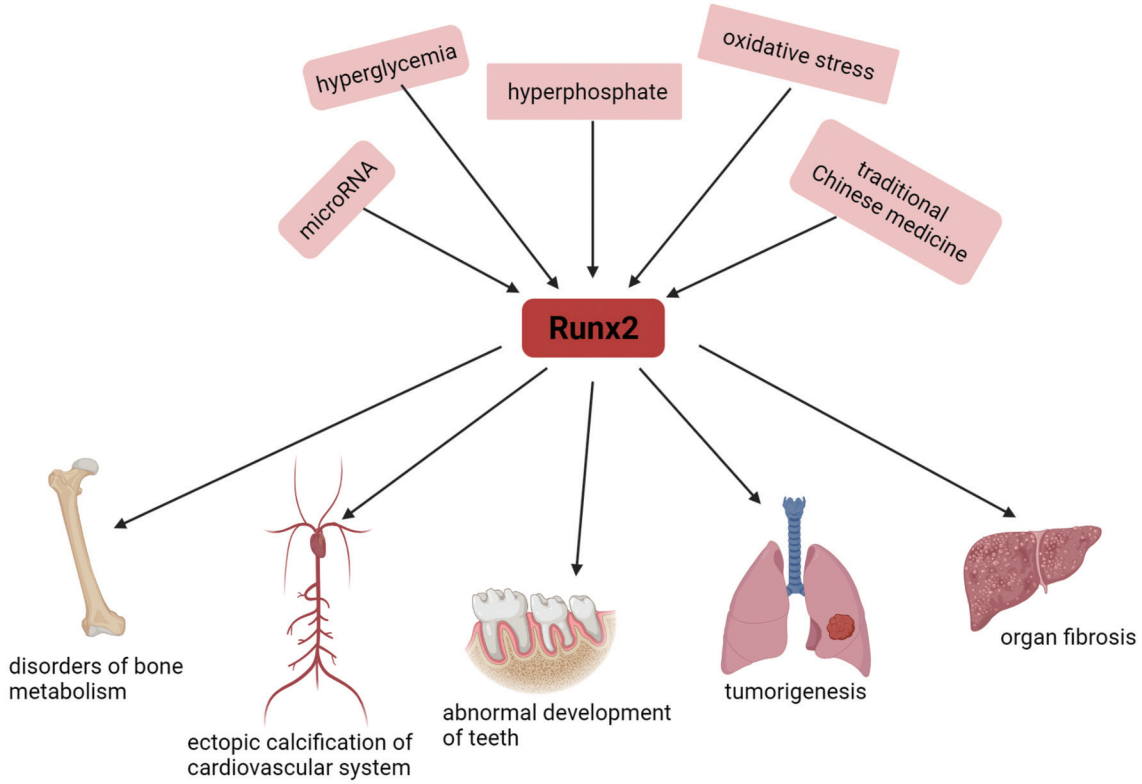

Fig. 1. Pathogenic potential of Runx2 The expression of Runx2 is regulated by several factors, such as microRNAs, traditional Chinese medicine, hyperglycemia, hyperphosphate, and oxidative stress. The dysregulated expression of Runx2 contributes to disorders of bone metabolism, ectopic calcification of cardiovascular system, abnormal development of teeth, tumorigenesis, and organ fibrosis.

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