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RESEARCH HIGHLIGHT

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Cell cycle-independent roles of p19^{INK4d} in human terminal erythropoiesis

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Normally, cyclin interacts with cyclin-dependent kinase (CDK) to form a cyclin-CDK complex, which promotes cell cycle progression, whereas cyclin-dependent kinase inhibitor (CDKI) molecules inhibit the formation of cyclin-CDK complex, arresting cell cycle. Terminal erythropoiesis is closely coordinated with cell cycle exit, which is regulated by cyclins, CDKs, and CDKIs [1]. In the global transcriptome of human terminal erythropoiesis [2], p19^{INK4d} is expressed highly, and its expression is significantly up-regulated during human terminal erythropoiesis. However, the roles of p19^{INK4d} in terminal erythropoiesis are still unknown.

As reported in our article recently published in *Blood* entitled "Unexpected roles for p19^{INK4d} in posttranscriptional regulation of GATA1 and modulation of human terminal erythropoiesis" [3], we demonstrated what roles p19^{INK4d} plays in human terminal erythropoiesis. We found that, in the erythropoietin-induced, CD34-positive hematopoietic stem cell (HSC) differentiation system, knockdown of p19^{INK4d} delays terminal erythroid differentiation, inhibits erythroblast growth due to increased apoptosis, and leads to the generation of abnormally nucleated late-stage erythroblasts. Unexpectedly, knockdown of p19^{INK4d} did not affect cell cycle, and these functions caused by p19^{INK4d} knockdown were via decreasing levels of GATA-binding protein 1 (GATA1). Furthermore, we found that p19^{INK4d} modulates GATA1 protein levels through a novel pathway, the phosphatidylethanolamine-binding protein 1 (PEBP1)-phosphorylated extracellular signal-regulated kinase (*p*ERK)-heat shock 70 kDa protein (HSP70)-GATA1 pathway [3].

As a classical CDKI member, p19^{INK4d} has been shown to inhibit the formation of cyclin D-CDK4/6 complex, arresting cell cycle in the G_0/G_1 phase [4]. p19^{INK4d} was often induced to inhibit the proliferation of many kinds of tumor cells, such as T cell acute lymphoblast leukemia cells and lung cancer H1299 cells [4, 5]. Additionally, deletion of p19^{INK4d} leads to the development of many tumors, including osteosarcomas [6] and anterior lobe tumors [7]. p19^{INK4d} is also involved in HSC quiescence, megakaryocyte differentiation, and granulocytic differentiation, which are closely associated with cell cycle arrest [8–10]. However, as shown in our study, p19^{INK4d} played important roles independent of cell cycle regulation, and the lack of cell cycle change was probably due to the compensatory up-regulation of p18^{INK4c} following p19^{INK4d} knockdown. Our findings provide greater understanding of the role that CDKIs play in cell cycle regulation.

In conclusion, our study revealed the cell cycle-independent roles of p19^{INK4d} in human terminal erythropoiesis via a novel PEBP1-*p*ERK-HSP70-GATA1 pathway. These findings will likely improve understanding of disordered erythropoiesis, including thalassemia, myelodysplastic syndrome, and congenital dyserythropoietic anemia, and guide future studies that focus on CDKIs.

Authors' contributions

XH wrote the manuscript. JL reviewed and revised the manuscript. Both authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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