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Cyclin A1 is a transcriptional target of PITX2 and overexpressed in papillary thyroid carcinoma

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Abstract Physiological expression of cyclin A1, a unique cell cycle regulator essential for spermatogenesis, is predominantly restricted in male germ cells. Outstandingly, previous studies have also demonstrated the abnormal expression of cyclin A1 in various human tumors. How male germ cell-specific cyclin A1 is transcriptionally activated in tumor cells, however, is elusive. To begin to understand the molecular mechanisms governing the ectopic expression of cyclin A1, we searched for transcription factors and cis-regulatory DNA elements. We found that overexpression of PITX2, a paired-like homeodomain transcription factor and a downstream effector of Wnt/β-catenin signaling, resulted in upregulation of cyclin A1 in HEK293 cells and TPC-1 thyroid cancer cells. On the other hand, PITX2 knockdown in TPC-1 cells caused reduced cyclin A1. Promoter reporter assays with a series of deletion constructs determined that the DNA element from −102 to −96 bp of the cyclin A1 promoter is responsible for PITX2-induced gene expression. The result of chromatin immunoprecipitation revealed the occupancy of PITX2 on the cyclin A1 promoter. Taken together, these findings demonstrate that cyclin A1 is a transcriptional target of PITX2. Consistently, our immunohistochemistry result showed up-regulation of cyclin A1 in human papillary thyroid carcinoma, where overexpressed PITX2 has been endorsed in our recent report. Thus, our study provides new evidence on the regulation of cyclin A1 gene expression and offers a PITX2-cycin A1 pathway for cell cycle regulation.

Keywords Cyclin A1 · PITX2 · Transcriptional regulation · Thyroid cancer

Introduction

Cyclins are a group of proteins concentration of which fluctuates in a cyclical fashion during the eukaryotic cell cycle [1]. A cyclin forms a complex with its cyclin-dependent kinase (CDK) partner, which results in the activation of the CDK. The activated cyclin/CDK complex then regulates cell cycle progression through phosphorylation of specific substrates. A-type cyclins, including cyclin A1 (CCNA1) and cyclin A2 (CCNA2, previously known as cyclin A), may interact with CDK1 and CDK2 [2–4]. Cyclin A2 is ubiquitously expressed and responsible for regulation of both G1-S and G2-M transitions by binding to CDK2 in S-phase and CDK1 in G2-phase of cell cycle, respectively [2, 3]. In contrast, cyclin A1 is predominantly expressed in male germ cells (specifically, late pachytene and diplotene spermatocytes) and is essential for the G2–M transition of meiosis I [5]. Recent report suggested that Sp1 and GATA1, the two transcription factors, might contribute to the repression of cyclin A1 expression in somatic cells [6].

Yan Liu and Yue Huang have equally contributed to this work.

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