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博 士 学 位 论 文

FOXO3 转录因子通过与 Cdt1蛋白相互作用调控细胞周期进展

Regulation of cell cycle progression by FOXO3 through its binding partner DNA replication factor Cdt1

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摘 要

为了维持基因组的稳定性，真核生物体必须保证在每个细胞周期中DNA有且仅有一次被复制。在各个复制起始位点形成前复制复合体（Pre-RC）是DNA复制的关键步骤。Cdt1是Pre-RC中的重要组成蛋白，Cdt1的蛋白水平受到精确调控，由此确保每个周期中DNA不发生重复复制（re-replication）。当细胞进入S期，Cdt1受到以下机制精确调节：首先，Geminin通过与Cdt1结合产生空间位阻作用，阻止Cdt1与MCM2-7结合，抑制其作为MCM2-7在DNA上停靠（load）的媒介功能。其次，SCF-Skp2、Cul4-DDB1和APC/C-Cdh1三个E3泛素化连接酶分别被报道可以识别并泛素化Cdt1，导致其通过蛋白酶体途径降解。在G2期和M期，Geminin与Cdt1形成复合物阻止其与E3泛素化连接酶结合，从而稳定Cdt1，为下一细胞周期做准备。值得注意的是，人们对在正常生理条件下正向调控Cdt1的机制还了解不多。在本文中，我们鉴定出Cdt1新的结合蛋白FOXO3，发现二者形成复合体，共同定位在细胞核中。FOXO3-Cdt1复合体可阻止Cdt1和DDB1以及Cdt1与PCNA的结合，从而抑制Cdt1被Cul4-DDB1泛素化，以及随后的蛋白酶体降解。在细胞中敲低FOXO3， Cdt1蛋白水解增加，细胞进入S期减少，细胞增殖减慢。我们通过对比FOXO3敲低细胞与Cdt1敲低细胞发现，这两种蛋白敲低的生物学表型非常相似，均影响细胞G1期至S期的转换。结合FOXO3对Cdt1蛋白的调控，这说明FOXO3和Cdt1在细胞周期调控上具有相关性。在FOXO3敲低细胞中，Geminin水平也降低，但这并不是FOXO3敲低直接引起的。Geminin敲低激活了DNA损伤检测点、导致DNA重复复制、细胞增殖减慢但并不发生G1期阻滞，这些表型与FOXO3敲低的表型有很大差异。由于Geminin和Cdt1在细胞周期中保持一定的平衡，FOXO3敲低细胞中Geminin水平下降很可能是由于Cdt1水平下降间接导致的。本论文揭示了FOXO3的一个全新功能，即通过蛋白-蛋白相互作用来维持Cdt1在细胞周期进展中的基础水平，从而调控G1期向S期的演进。

关键词：FOXO3;Cdt1;细胞周期

Abstract

To ensure genome stability, DNA must be replicated once and only once during each cell cycle. Replication licensing begins by the formation of the pre-replication complex (Pre-RC) at multiple potential origins of replication. As one of the major components of Pre-RC, Cdt1 is tightly regulated to make sure that cells do not rereplicate their DNA. Multiple regulatory mechanisms operate to ensure degradation of Cdt1 in S phase. First, Geminin negatively regulates Cdt1 function by prevention of the association of Cdt1 with MCM2–7 via steric hindrance. Second, Cdt1 is targeted for proteolysis by three distinct ubiquitin E3 ligases, the SCF-Skp2 complex, the DDB1-Cul4 complex and the APC/C-Cdh1 complex. However, in G2 and M phases, Geminin positively regulates Cdt1 by preventing its ubiquitylation, perhaps by prevention of its interaction with an E3 ligase. Even so, little is known about the positive regulators of Cdt1 under physiological conditions. Here we identify FOXO3 as a binding partner of Cdt1. FOXO3 forms a protein complex with Cdt1, which in turn blocks its interaction with DDB1 and PCNA. Conversely, FOXO3 depletion facilitated the proteolysis of Cdt1 in unperturbed cells. Intriguingly, FOXO3 deﬁciency resulted in impaired S-phase entry and reduced cell proliferation. We provide data that FOXO3 knockdown mimics Cdt1 down-regulation and affects G1/S transitions. Endogenous Geminin levels were also decreased in our FOXO3-depleted cells, but it is secondary to FOXO3-mediated Cdt1 destabilization. Our results demonstrate a unique role of FOXO3 in binding to Cdt1 and maintaining its level required for cell cycle progression.

Keywords: FOXO3;Cdt1;Cell cycle

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