Research Highlight

PCL2, a novel tumor suppressor in breast cancer

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Polycomb group (PcG) proteins were originally identified as suppressors of the homeotic genes in Drosophila [1], controlling segment identity during embryonic development. Then PcG proteins were found to participate in the regulation of various biologic processes, including cell cycle, apoptosis and tumor development [2]. It is commonly accepted that the PcG proteins form two major evolutionarily conserved Polycomb Repressive Complexes (PRCs). The Polycomb Repressive Complexes 1 (PRC1) is mainly composed with BMI1, MEL18, RING1, and CBX, which could catalyze mono-ubiquitination of H2AK119. PRC2 mainly contains EZH2, SUZ12, and EED, which is responsible for catalyzing H3K27me3 [3]. Histone H3 lysine 27 trimethylation (H3K27me3) is a marker for gene silencing, and the enzymatic activity of PRC2 made it significant in various processes, such as stem cell renewal, differentiation, and cancer progression.

Besides the core members of PRC2, several PRC2-associated factors are needed to enhance the enzymatic activity [4], help to recognize the genomic regions, or stabilize the combination between target genes and PRC2. Polycomblike (PCL) proteins are firstly recognized in D. melanogaster, and named by the same phenotype as PcG proteins after gene mutant. In mammal, there are three homologs, namely PHF1/PCL1, MTF2/PCL2, and PHF19/PCL3 [5]. PCL proteins are Polycomb repressive complex 2 (PRC2)-associated factors; and involved in transcriptional repression. All of the three PCL proteins possess a Tudor domain and two plant homeodomain (PHD) fingers, which are required for target gene recognition and combination. Recent study revealed that PCL proteins have major role in PRC2 recruitment to CpG islands [6]. In addition, the Tudor domains of PCL proteins are crucial for PRC2 spreading on chromatin [7]. Many studies focused on the role of Polycomblike proteins in regulating the left-right asymmetry [8] and self-renewal and differentiation of embryonic stem cells [9], few studies investigated the role and related mechanisms of PCL proteins in cancer. PCL1 was involved in the response to DNA double-strand breaks through interacting with ku70/ku80 [10]. Subsequent studies showed that PCL1 was able to stabilize p53 expression through directly combing with p53 and inhibiting MDM2-mediated nuclear export of p53 [11]. PCL3 was found to be overexpressed in many cancers and may be involved in tumor progression [12]. As for PCL2, deletion of PCL2 in ESCs led to decreased level of H3K27me3 at specific pluripotency-related factors [13], causing disturbed genic environment. Given the facts that ESCs and tumor cells bear many similar characteristics, PCL2 dysregulation might lead to formation of cancer stem cells, ultimately causing the development of heterogeneous tumor. Previously, Li et al demonstrated that PCL2 could promote cellular senescence through elevating the expression of Cdkn2a, preliminarily reveling the role of PCL2 in cancer [14]. In this study “PCL2 regulates p53 stability and functions as a tumor suppressor in breast cancer in breast cancer” [15]. Dr. Li provides further evidence for the potential role of PCL2 in cancer and proposes a new view for PCL2 in breast cancer research.

Breast cancers are the most common malignant tumor and the first leading cause of cancer death in women. It has been demonstrated that PCL2 downregulation in breast cancer is associated with better prognosis. Using in vitro and in vivo tools, Li and colleagues have identified a novel function for PCL2 in regulating proliferation, apoptosis, and migration of breast cancer, indicating that PCL2 may act as a tumor suppressor. Abnormal expression of P53 has been implicated in the genesis and development of many types of cancer. Stabilizing p53 and p53 accumulation in the nucleus could contribute to induce the cell cycle arrest or apoptosis [16]. Through comprehensive and integrated experiments, the authors designate that PCL2 may have important function in regulating p53 stability. Different from PCL1 and PCL2, who mainly located in nucleus, the main subcellular location of PCL2 was nucleolus, providing a novel and interesting mechanism for p53 stabilization. PCL2 was able to combine with both p53 and MDM2, moreover, PCL2 co-localized with MDM2 and limited MDM2 in the nucleolus. Thus, PCL2 could protect p53 from combing with MDM2 and inhibit MDM2-mediated ubiquitination of p53 (Fig. 1). Overall, with well-designed experiments, Dr. Li and colleagues uncovered the novel function of PCL2 in breast cancer and might contribute to the potential application in future tumor treatment.

Conflict of interest

The author declares that he has no conflict of interest.
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References