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The cyclin K/Cdk12 complex

An emerging new player in the maintenance of genome stability

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Maintenance of genome stability is essential for cell survival and protection from various diseases, including cancer. Genome instability is a consequence of the accumulation of various DNA lesions induced either by normal endogenous processes, such as cellular metabolism, or exogenously by radiation and toxic chemicals. The DNA damage response (DDR) is an evolutionarily conserved mechanism that maintains genome stability by detection and repair of DNA lesions. The DDR is mediated by networks of hundreds of proteins that detect and signal DNA damage and recruit or activate effector proteins to repair DNA lesions. Due to intensive efforts of many laboratories and development of genome-wide screens during the last decade, many new players and pathways mediating genome stability have been identified. These include, among others, transcriptional cyclin-dependent kinase (Cdk) complexes and phosphorylation of the C-terminal domain (CTD) of RNA polymerase II (RNAPII).

In a recent study, we reported that the cyclin K/cyclin-dependent kinase 12 (CycK/Cdk12) complex maintains genome stability via regulation of expression of DDR genes. Cells depleted of the CycK/Cdk12 complex showed decreased expression of several critical regulators of genome stability, specifically, BRCA1, ATR, FANCI and FANCD2 proteins. Complementing this result, silencing of the CycK/Cdk12 complex caused increased numbers of the 53BP1 and γH2AX foci, markers of spontaneous DNA damage signaling. Also, the DNA damage cell cycle checkpoint was activated, as indicated by the increased numbers of cells accumulated in the G_2-M phase. Finally, loss of the CycK/Cdk12 complex rendered cells sensitive to various DNA damaging agents, including camptothecin, etoposide and mitomycin C.[1]

Although determination of the precise defect in the expression of DDR genes needs more research, lower abundance of nascent mRNA on BRCA1, ATR and FANCI genes and decreased amounts of RNAPII on their promoters in the absence of the CycK/Cdk12 complex point to an aberrant transcription.[1] Since the expression of predominantly long and complex genes is dependent on the CycK/Cdk12 complex, abnormal mRNA processing might also be involved. Interestingly, recent research found a widespread role of mRNA processing factors in mediating genome stability.[2] Although it was suggested that Cdk12 is involved in the regulation of alternative splicing,[3] we have not detected any splicing defect on splicing-sensitive microarrays for almost all DDR genes downregulated in the absence of the CycK/Cdk12 complex.[1]

Until recently, it was assumed that CycK is an alternative cyclin subunit of Cdk9, and that Cdk12 binds cyclin L. A recent study showed that Drosophila Cdk12 binds CycK and, with Cdk12 in mammals, is a homolog of Ctk1 in yeast, itself previously thought to be a Cdk9 homolog.[4] Our work established CycK to be a bona fide partner of Cdk12 in human cells,[1] and we also confirmed the results from Bartkowiak et al. that CycK/Cdk12 is a major kinase of serine 2 (Ser2) in the CTD of RNAPII.[1,4] Notably, the CTD of RNAPII was functionally linked to the DDR by the regulation of several cellular processes, such as transcription, mRNA processing and recombination. For example, in human cells, phosphorylation of the CTD directed the response to DNA damage by the regulation of alternative splicing,[5] and CTD-associated protein RecQ5 was important for the control of transcription-associated genome stability.[6] In yeast, following DNA damage, the phosphorylation of Ser2 in the CTD and transcription of several DNA damage repair genes is dependent on Ctk1.[7] Thus, evidence is accumulating that the CTD and its posttranslational modifications, associated proteins and modifying enzymes are emerging as new players in cellular response to DNA damage.

In accordance with the role of Cdk12 in the maintenance of genome stability is the finding that Cdk12 is one of the most often somatically mutated genes in ovarian cancer.[8] All of the missense mutations identified were clustered in its kinase domain, suggesting that phosphorylation of the CTD of RNAPII might be indeed critical for the function of Cdk12 in this devastating disease. About half of the ovarian tumors were defective in homologous recombination (HR),[8] and since Cdk12 depletion leads to downregulation of several crucial HR regulators [specifically, BRCA1,[1] ATM and RAD51 (Blazek D, unpublished data)], aberrant HR may be the driving force in Cdk12-dependent ovarian carcinoma. Notably, the Cdk12 gene was found to be co-amplified with the tyrosine kinase receptor ERBB2, a protein frequently overexpressed in breast cancer.[9] Gene fusion of Cdk12-ERBB2 was also identified in gastric cancer.[10]

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Thus, the role of the CycK/Cdk12 complex in the maintenance of genome stability is clearly emerging, which is consistent with the dysregulation of Cdk12 in various tumors. Future characterization of the CycK/Cdk12 complex should reveal the precise mechanism that regulates its physiological function, the disruption of which leads to development of a pathological state.

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