p38 MAPK renders RB resistant to inactivation by CDKs

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Abstract

The main function of the tumor suppressor Retinoblastoma (RB) is the regulation of the G1/S phase transition. This event is critical for the proliferation of normal cells in tissues, and its inhibition is one of the most important hallmarks leading to cancer. In resting cells RB is unphosphorylated and represses E2F-mediated gene expression. Upon entry into cell cycle, Rb becomes phosphorylated at the C-term through the action of Cyclin-Cdk complexes thus leading to its inactivation and the transcription of essential genes for S phase entry. Upon stress, cells deploy different mechanisms in order to adapt and increase their chances of survival. Among these, the control of cell division is essential. It is well established that stress-activated protein kinases (SAPKs) such as p38 play a key role in cell cycle regulation. During the G1-S transition, p38 regulates essential components of the cell cycle machinery such as the cyclin-dependent kinase (CDK) inhibitors p21Cip1, p27Kip1and p57Kip2. The CDK inhibitor p57Kip2 is phosphorylated by p38 which enhances its association to CDK2-Cyclin complexes and leads to reduced CDK2 activity. As a consequence, cells transiently arrest at the G1 cell phase [1]. However, stressed p57Kip2 knockout cells are still able, albeit to a lesser extent, to delay G1, which is an indication that other mechanisms involved in cell cycle control exist. Remarkably, upon stress, p38 also inhibits the transcription of E2F-dependent genes, which are necessary for cell cycle progression. These results prompted us to question whether p38 might be controlling Rb activity. Our results show that, upon stress p38 phosphorylates the N-term of Retinoblastoma (RB), making RB insensitive to cyclin-dependent kinase (CDK)-Cyclin inactivation and increases its affinity toward the E2F transcription factor, thus repressing E2F-mediated gene expression and delaying cell-cycle progression [2,3].This novel mechanism of RB regulation represents an opportunity for developing new cancer drug treatments for tumors by developing compounds capable of promoting the association of E2F transcription factors to the N-term of RB.

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