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Cdk2 regulates metastasis suppressor BRMS1

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CDKs (cyclin dependent kinases) are master regulators of cell cycle. Each CDK is activated by a cyclin protein to drive progression through phases of the cell cycle: cyclin D-CDK4/6 responds downstream of mitogenic signals to phosphorylate Rb and begin DNA synthesis, cyclin E/CDK2 completes the phosphorylation of Rb and drives progression through S phase, cyclin A/CDK2 completes S phase and cyclin A/CDK1 and cyclin B/CDK1 complexes drives entry into and progression through mitosis. The sequential activation of each cyclin/CDK complex is essential for the temporal control of cell cycle events to ensure a successful cell division, and this includes CDKmediated synchronization of the cell cycle with non-cell cycle functions, often via phosphorylation of these targets.

Large-scale studies of phosphorylation targets and interacting partners for CDKs have identified many targets outside the traditional ambit of the cell cycle.[1,2] CDKs interact with and phosphorylate hundreds of different proteins, including proteins that act in DNA damage, intracellular transport, protein degradation, signal transduction, DNA and RNA metabolism and translation. For the most part the functional consequence of these interactions and phosphorylations has not been characterized, though recent work has shown novel functions for CDK1 and CDK2 in epigenetic regulation and the non-cell cycle CDK, CDK5, in neuronal function including synaptic vesicle trafficking.[2]

Roesley et al [3] have now identified a novel link between CDK2 and cell migration by characterizing the CDK2-mediated phosphorylation of BRMS1. BRMS1 (or breast cancer metastasis suppressor 1) associates with histone deactylase complexes that remodel chromatin, as well as acting as a transcriptional repressor. Through these functions BRMS1 strongly represses invasion and metastasis, though without any effect on primary tumorigenesis. Roesley et al show that CDK2 phosphorylates BRMS1 on Serine 237, and mutation of this residue prevents BRMS1 from suppressing cell migration. Consistent with our current knowledge of BRMS1 as a metastasis suppressor that does not influence primary tumor growth, Roesley et al also show that overexpression of BRMS1 S237D (which mimics the constitutively phosphorylated protein) did not suppress the proliferation or colony forming potential of cancer cells.[3]

This is an important finding as it suggests that high CDK2 activity may suppress invasion and metastasis via BRMS1, though paradoxically high CDK2 activity is normally assumed to be tumorigenic. However, since the initiation of a primary tumor and metastasis are distinct processes, it is not surprising that multifunctional master regulators such as cyclins and CDKs can play different roles in these disease stages, resulting in temporal changes to their expression as disease progresses.[4] The activation of BRMS1 by Cdk2 also makes rational sense for nontransformed cells: a cell engaging in a somatic cell division may downregulate migratory signals to prevent inappropriate invasion into adjacent tissues. However the effect of CDKs on cell migration is complex and may be context specific. For example, phosphorylation of SIRT2 by CDK2 antagonizes SIRT2-mediated inhibition of fibroblast cell migration [5] and CDK5 activity increases the motility of endothelial cells.[6]

There are still open questions about how S237 phosphorylation alters the function of BRMS1, as mutation of this site does not affect BRMS1 localization, binding to the HDAC complex or RBP1 protein, or the transcriptional regulation of osteopontin by BRMS1.[3] As observed by the authors, the S237 site is immediately proximate to the site of an NLS2 putative nuclear localization signal which is known to be important to the ability of BRMS1 to suppress metastasis, and this bears further investigation. More recently, it has been found that BRMS1 acts as a ubiquitin ligase toward the p300 histone acetyltransferase where alteration of this ubiquitin ligase activity increases metastasis,[7] and this is another possible function of BRMS1 that may be modulated by S237 phosphorylation. As we gain more understanding of the diverse functions of BRMS1 there will be an opportunity to examine how CDK activity influences BRMS1-mediated suppression of metastasis.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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