COMMENT
Phosphatase, pseudo-phosphatase, or both? Understanding PRL oncogenicity

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Phosphatases of regenerating liver (PRL1–3) are among the most oncogenic protein phosphatases but their mechanism of action is poorly understood. Multiple substrates have been proposed as well as a non-catalytic function regulating magnesium transport. Our recent identification of a catalytically inactive PRL mutant that retains oncogenicity in a mouse model promises to resolve the question of whether PRLs act as phosphatases or pseudo-phosphatases in different cancer models.

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Fig. 1 PRL3 acts as a pseudo-phosphatase. Left to right: substitution of the catalytic cysteine 104 by aspartic acid preserves the negative charge required for CNNM binding but abolishes PRL3 catalytic activity. Both wild-type and mutant PRLs can bind CNNM proteins to inhibit magnesium efflux. Analysis of the C104D mutant in the B16 melanoma mouse model shows that CNNM binding is necessary and sufficient for PRL3-driven tumour metastasis.10

behave both as pseudo-phosphatases and phosphatases. They regulate CNNM proteins via direct binding but are themselves regulated through their catalytic activity.

Cysteine oxidation probably provides an additional level of regulation of the PRL–CNNM interaction. Little is known about the oxidation state in cells, but the purified PRL proteins are partially oxidised even in mildly reducing conditions.6 The disulphide forms of PRLs show approximately 1000-fold weaker binding to CNNM proteins and, of course, are catalytically inactive.7 An increase in reactive oxygen species would be expected to decrease CNNM binding and intracellular magnesium levels, possibly as a homeostatic feedback loop to regulate mitochondrial metabolism.

Going forward, many questions remain to be answered. PRL expression levels are greatly increased in metastatic cancer and regenerating liver cells, but nothing is known about the signals that control PRL phosphorylation and oxidation. In cultured cells, PRL phosphorylation changes dramatically in response to magnesium availability but the mechanism and substrates involved are unknown. Finally, much more needs to be done to understand how changes in magnesium efflux lead to downstream effects and cancer metastasis. One point that is clear is that the PRL mutations that selectively impair phosphatase or pseudo-phosphatase activities will be valuable tools for future studies.

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AUTHOR CONTRIBUTIONS

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