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METABOLISM

MAD interactions with insulin receptor

> MCC proteins are important regulators of insulin signalling

Insulin signalling regulates systemic glucose metabolism and its dysregulation leads to metabolic disorders, including diabetes. Choi *et al.* reveal that proteins of the mitotic checkpoint complex (MCC), which normally function to ensure accurate chromosome segregation during mitosis, have important roles in insulin signalling by regulating the endocytosis of insulin receptors.

Choi *et al.* generated knockout mice, in which the negative regulator of MCC p31^{comet} (also known as MAD2L1BP) was deleted. Unexpectedly, they found that, instead of the anticipated increase in genome instability and thus tumorigenesis susceptibility owing to MCC misregulation, these mice exhibited neonatal lethality associated with metabolic defects, most notably reduced glycogen storage in the liver. Liver-specific knockout mice indicated that the loss of p31^{comet} in hepatocytes interfered with insulin receptor activation, thereby leading to impaired glycogen synthesis, systemic hyperglycaemia and insulin resistance.

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When analysing the effects of p31^{comet} loss in mouse hepatocytes *in vivo* and in human hepatocellular carcinoma HepG2 cells, the authors found that insulin receptors localized to intracellular vesicles rather than to the plasma membrane. Blocking clathrin-mediated endocytosis rescued this aberrant receptor localization, indicating that p31^{comet} expression is important to regulate insulin receptor internalization through endocytosis.

To further dissect the role of MCC proteins in insulin receptor internalization, the authors investigated the involvement of MAD2 (also known as MAD2L1), a binding partner of p31^{comet}. Biochemical studies revealed that MAD2 and the insulin receptor directly interact; abolishing this interaction by introducing mutations in the MAD2-interacting motif (MIM) prevented insulin receptor endocytosis. Importantly, expression of MIM-mutant insulin receptors was able to restore insulin signalling in the p31^{comet}-knockout hepatocytes, and improved insulin and glucose tolerance of knockout mice.

For MCC activation, MAD2 interacts with BUB1-related protein kinase (BUBR1; also known as BUB1B), and this interaction is inhibited by p31^{comet}, leading to MCC inactivation. Similar to the interactions established during MCC inactivation, Choi *et al.* found that p31^{comet} was important for inhibiting the interaction between BUBR1 and insulin receptor-bound MAD2 at the plasma membrane. As BUBR1 has been previously shown to interact with adaptor protein 2 (AP2), which bridges clathrin and cargo for endocytosis, the authors propose that MAD2, together with BUBR1, recruits AP2 to the insulin receptors localized at the plasma membrane, inducing their clathrin-mediated endocytosis; p31^{comet} regulates this process by inhibiting the interaction between MAD2 and BUBR1 to prevent precocious internalization of non-stimulated insulin receptors.

In this study, Choi *et al.* provide new insights into the mechanisms underlying insulin resistance by revealing that MCC proteins are important regulators of insulin signalling. How this novel metabolic function of mitotic checkpoint regulators is controlled and whether the mitotic and metabolic roles of these proteins are functionally linked remain to be elucidated.

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