Mitotic Checkpoint Regulators in Insulin Signaling

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Insulin regulates glucose and lipid metabolism and cell growth in multiple tissues, and impacts many facets of animal physiology. Dysregulation of insulin signaling causes metabolic disorders, including diabetes. The spindle checkpoint ensures accurate chromosome segregation during mitosis and suppresses aneuploidy. The checkpoint proteins MAD2 and BUBR1 interact with CDC20 to form the mitotic checkpoint complex (MCC), which prevents premature anaphase onset. The Mad2 inhibitor $p31^{comet}$ promotes MCC disassembly, checkpoint inactivation, and timely chromosome segregation. We have recently discovered that the MAD2-BUBR1-$p31^{comet}$ module controls clathrin-mediated endocytosis of insulin receptor (IR), and genetic ablation of $p31^{comet}$ in mice causes premature IR endocytosis and insulin resistance. Here, we report two cooperative mechanisms for recruiting the clathrin adaptor AP2 to IR to initiate its endocytosis. MAD2, BUBR1, and CDC20 assemble an MCC-like complex on IR and provide one AP2-contacting site. $p31^{comet}$ inhibits IR endocytosis through blocking the assembly of this IR-MCC complex. Insulin receptor substrate 1 and 2 (IRS1/2) bound to the activated IR provide the second AP2-binding site. The IRS1/2-AP2 interaction requires stimulatory MAP kinase-dependent phosphorylation on IRS1/2 and subsequent removal of inhibitory phosphorylation by the tyrosine phosphatase SHP2. This feedback regulation ensures that IR endocytosis only occurs after the execution of downstream events. Knock-in mice harboring mutant IR alleles deficient for MAD2 binding are resistant to diet-induced obesity and insulin resistance. The IR plasma membrane levels in liver biopsies from human type 2 diabetes patients are lower than those in non-diabetes controls. We propose that prolonging IR action at the cell surface by genetic or chemical inhibition of IR internalization may hold promise for the treatment of type 2 diabetes.