Glycogen localisation of AMPK is a regulated process

AMP-activated protein kinase (AMPK) is a metabolic master kinase that plays a key role in maintaining energy homeostasis at cellular and whole body level. Recent evidence links AMPK activation to health benefits, such as increased longevity and reduced ageing-related diseases.

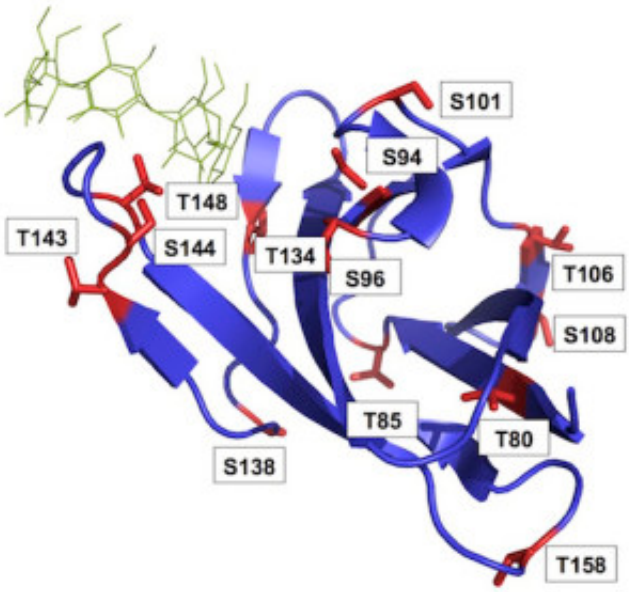

Fig. 1. X-ray structure of the ?-subunit carbohydrate-binding module (CBM) in complex with the cyclic sugar ?-cyclodextrin. All serine (S) and threonine (T) residues of the CBM are indicated. Note the situation of threonine 148 central in the binding site, which explains the phosphorylation as a mediator of the loss of sugar-binding affinity.

AMPK is an enzyme that forms an obligatory ??? heterotrimer. The ?-subunit is a catalytic subunit that carries the threonine-172 phosphorylation site within the kinase domain. The ?-subunit allows AMPK to sense changes in adenine nucleotides, thereby indirectly regulating AMPK activity, whereas the regulatory ?-subunit is responsible for localization to glycogen owing to a carbohydrate-binding module (CBM) being part of the ?-subunit. However, various studies have shown that AMPK is found in different subcellularlocalizations, such as nucleus where glycogen is not found. Therefore, it remained unexplained how AMPK can dissociate from glycogen.

We recently identified a molecular mechanism that prevents AMPK from binding to glycogen. Glycogen depletion causes the release of AMPK to the cytosol, which occurs in conjunction with AMPK activation. Using cell-free carbohydrate-binding assays, our data revealed that AMPK autophosphorylation rather than AMPK activation is involved in the regulation of AMPK–glycogen binding. Structural data disclosed the presence of the threonine-148 (Thr-148) residue that is

centrally situated in the carbohydrate-binding pocket (Figure 1). Substitution of Thr-148 to a phospho-mimicking aspartate (T148D) resulted in loss of carbohydrate-binding ability of the AMPK-?-CBM in cell-free assays. Cellular immunofluorescence studies confirmed that the T148D mutant had lost its capability of binding to intracellular glycogen, whereas wild-type CBM localizes to glycogen particles. Breakdown of glycogen, which was induced by lowering glucose availability and/or pharmacological activation of AMPK, enhanced the phosphorylation of Thr-148. In comparison to overexpression of AMPK-?-T148D, the intracellular glycogen content was reduced with wild-type AMPKoverexpression, if cells were challenged with AMPK activating stimuli. Altogether, these data disclose the phosphorylation of Thr-148 of AMPK-? as a novel mechanism that excludes AMPK from binding to glycogen. Further studies are needed to unravel the roles of AMPK and Thr-148 phosphorylation in skeletal muscle and liver, where the bulk amounts of glycogen are stored in the human body.

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Publication

The recruitment of AMP-activated protein kinase to glycogen is regulated by autophosphorylation.
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