The role of feedback mechanisms in biological processes regulated by Snf1/AMPK

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Abstract:
Feedback mechanisms are primary known processes for robust homeostatic regulation of biological systems. Studying the principles that enable such regulations is critical to better elucidate fundamental topics in cellular biology.
Snf1/AMPK is a member of a conserved family of serine/threonine kinases involved in maintaining energy homeostasis. In *Saccharomyces cerevisiae* Snf1/AMPK responds to cellular stresses, such as nutrient limitation, regulating pathways involved in the metabolism of different carbon sources (Coccetti et al, 2018).

Our recent results showed that the regulation of Snf1/AMPK depends on feedback mechanisms and we are now investigating two proteins that could be involved in it. The first one is Sak1, one of its activating kinases, while the second one is the regulatory β subunit Sip2, which regulates the localization of the Snf1/AMPK complex.

Through a SILAC-based phosphoproteomic analysis, in collaboration with the group of Prof. Claudio De Virgilio (Fribourg, Switzerland), we observed previously undetected Snf1/AMPK-dependent phosphosites on Sak1 and Sip2 proteins, which could be the key to identify this feedback regulation. Indeed, we hypothesize that this phosphorylations have an autoregulatory function on the activity of Snf1/AMPK. When phosphorylated, both Sak1 and Sip2 show a negative feedback mechanism that switches off Snf1/AMPK activity when no longer needed.

Understanding the regulation of this kinase, along with its homolog in mammals AMPK, results crucial because of its role not only in metabolism and stress response, but also in the control of growth and proliferation (Hedbacker and Carlson, 2008). These are key processes for cell viability and also important to regulate aging and prevent alterations that can bring to human diseases (Jeon, 2016, Coccetti et al., 2018).