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Commentary Open Access

CDKs: Much More Than Just the Control of Cell Cycle Progression

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Abstract

Lee and colleagues have shown that CDK4 plays a central role in glucose homeostasis. Insulin activates cyclin D1–CDK4, leading to a decrease in circulating glucose as a consequence of the down-regulation of main genes involved in liver gluconeogenesis.

Commentary

In recent years, our knowledge of CDK regulation has improved significantly and is no longer restricted to just its role in the control of cell cycle progression. Cyclin-dependent kinases (CDKs) are serine/threonine protein kinases that are associated with their specific partners, cyclins which phosphorylate their protein targets. Thus, the cyclin-CDK complex works as a holoenzyme. The control of cell cycle progression by cyclin-CDK complexes was first studied several years ago, in the context of high proliferation rates and cancer. Understanding how CDKs function was one of the main aims of these studies, as the loss of this regulation can alter cell proliferation rates which, in the worst case scenario, may translate into malignant tumours.

The cell cycle is mainly divided into G1, S, G2, and M phases, and transition between these phases is strongly controlled. Transition from G1 to S is tightly regulated and depends on the activity of the G1 phase cyclin-CDK complexes, where CDK can be CDK4 or CDK6 and is associated with G1 D-type cyclins (D1, D2 and D3). In addition, there is an upper-level control of the activity of cyclin-CDK complexes determined by the presence or absence of two families of CDK inhibitors (CKIs), INK4 proteins and the Cip/Kip family, respectively. When the G1 phase cyclin-CDK complexes are active, they regulate the transition to the S phase by a direct phosphorylation of the retinoblastoma protein (Rb). Rb hyperphosphorylation mediates the release of the E2F transcription factor, allowing its transit to the nucleus, where it can promote the transcription of several genes involved in cell cycle progression, apoptosis, and DNA synthesis [1].

Besides their well-described role in the control of cell cycle progression, in recent years a new role for CDKs has emerged beyond the context of cell cycle progression, as a master regulator of metabolism. In this sense, the CDK4-RB-E2F axis and other cell cycle components have acquired a main role in the control of insulin secretion by pancreatic β-cells [2,3], of oxidative metabolism [4] and of adipogenesis [5-8].

Much more recently, a unique study designed by the Puigserver group [9] demonstrated that CDK4 plays a central role in glucose homeostasis, specifically in liver gluconeogenesis. Briefly, insulin activates AKT (also known as PKB) through a cascade of correlative phosphorylation with the insulin receptor, insulin receptor substrates, PI3K and finally PDK1 (Figure 1). Once AKT is activated, AKT phosphorylates several substrates, among them, Glycogen synthase kinase 3 (GSK3), at Ser 21 in α subunit and at Ser 9 in β subunit, resulting in the inhibition of GSK3 kinase activity [10-13]. GSK3 is a well-conserved kinase, originally identified as an enzyme that regulates glycogen synthesis in response to insulin [**14**].Further studies have demonstrated that GSK3 phosphorylates a broad range of substrates, including several transcription factors [15,16]. Moreover, GSK3 was eventually identified as being capable of phosphorylating cyclin D1 on T286 and inducing its rapid turnover in a proteasomal-dependent manner [17,18]. Consequently, GSK3 inhibition by AKT phosphorylation leads to an accumulation of cyclin D1.Furthermore, Lee et al. have demonstrated the increased mRNA expression of cyclin D1 after re-feeding, with amino acids specifically responsible for enhancing cyclin D1 mRNA levels [9] and (Figure 1). However, the molecular mechanisms underlying this increase remain elusive. Thus, we consider that it is necessary to investigate which amino acid oracids are responsible for cyclin D1 overexpression in hepatocytes after feeding. Subsequently, this knowledge may lead to the development of non-invasive therapies to control liver gluconeogenesis.

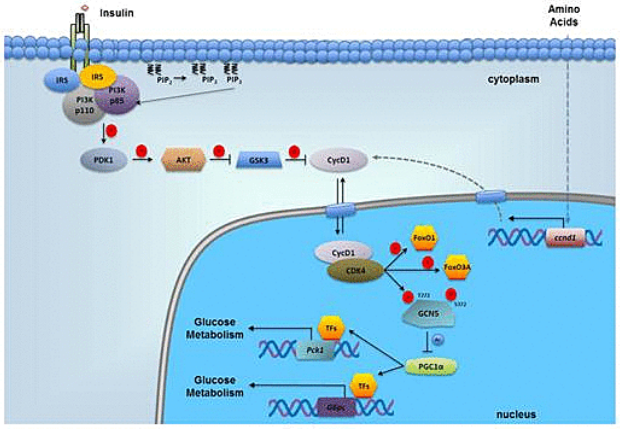

Figure 1: Schematic diagram showing the regulation of gluconeogenesis by CDK4 in liver. Adapted from (10)

The scenario described above promotes an activation of the holoenzyme cyclin D1–CDK4, which translates into decreased circulating glucose as a consequence of the inhibited expression of main genes involved in liver gluconeogenesis, namely Pck1 and G6pc. Expression of Pck1 and G6pc is mainly regulated by PGC-1α (peroxisome-proliferator-activated receptor-γ-coactivator-1α), whose activity is regulated by acetylation (inhibition) and deacetylation (activation).The histone deacetyl transferasesirtuin 1 (SIRT-1) deacetylates and activates PGC-1α [19],whereas GCN5 (general control non-repressed protein 5) acetylates PGC-1α and represses its co-transcriptional activity [20].

Activation of cyclin D1-CDK4 by insulin does not affect SIRT-1 activity. On the contrary, once the CDK4-cyclin D1 complex is active, this directly phosphorylates GCN5, increasing its acetyl transferase activity and suppressing hepatic glucose production by acetylation and inhibition of PGC-1α, which, in turn, inhibits the transcription of gluconeogenic genes (Figure 1). These results were corroborated with several molecular strategies: knock-down experiments, the use of non-phosphorytable GCN5 alleles, CDK4 chemical inhibition, and the use of different cyclin D1mutants. Consequently, the loss of holoenzyme activity resulted inaugmented gluconeogenesis and in higher levels of circulating glucose. In addition, in many *in vivo* studies, an involvement of PPARs was observed in the regulation of energy metabolism by the liver [21,22].

These discoveries indicate a potential crosstalk between the proteins of cell cycle control and metabolic machinery. Very recently, Lee and colleagues [9] contributed striking evidence toward these discoveries. They ingeniously showed using cells and animal models that insulin is capable of activating cell cycle machinery in hepatocytes to control glucose homeostasis. Thus, a new rolefor CDKs emerges, independently of previous ones related to cell division. This fact, combined with the role of CDK4 in pancreatic β-cell proliferation and insulin secretion, points to cell cycle machinery as a central regulator of systemic glucose homeostasis.

Many interesting questions remain open, and answering them can help provide a more complete view of CDK control in liver gluconeogenesis. Future investigations should determine whether CDK4 phosphorylations over FoxO3A trigger any physiological effects, perhaps modifying in some way cyclin D1 expression and consequently affecting CDK4 activity. Another point to consider is if the implication of CDKs is restricted to liver gluconeogenesis or if they are also involved in the metabolic regulation of other tissues such as skeletal muscle or adipose tissue. Finally, another unanswered question is if CDK6, also activated by D type cyclins, may play a similar role in the liver.

These results open a new field of research aimed at deciphering the metabolic functions of cell cycle components, as well as, in an opposing manner, the regulation of cell cycle progression by metabolic genes, not only in the liver but also in other organs and tissues. A greater understanding of CDKs may pave the way for developing the use of these proteins as therapeutic targets for metabolic diseases.

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