Linking metabolism and cell cycle progression via the APC/C<sup>Cdh1</sup> and SCF<sup>βTrCP</sup> ubiquitin ligases

Shanshan Duan<sup>a,b</sup> and Michele Pagano<sup>a,b,1</sup>

<sup>a</sup>Department of Pathology, NYU Cancer Institute, New York University School of Medicine, New York, NY 10016; and <sup>b</sup>Howard Hughes Medical Institute, New York University School of Medicine, New York, NY 10016

A n emerging hallmark of cancer cells is the reprogramming of energy metabolism pathways (1). By using the aerobic glycolysis pathway, cancer cells metabolize glucose at higher rates than normal tissues and convert it to lactate, a phenomenon known as the Warburg effect (2). Additionally, cancer cells have been reported to have increased glutamine metabolism, which exceeds the metabolic use of other non-essential amino acids (2). This altered metabolism fuels the growth and proliferation of cancer cells by providing energy and macromolecular building blocks, and it also contributes to the maintenance of redox balance (3, 4). A report in PNAS (5) provides evidence for how glucose and glutamine metabolism are regulated during cell cycle progression.

Metabolic activity is a major determinant of a cell’s “decision” to proliferate or exit the cell cycle to enter into a quiescent state, and accumulating evidence now suggests that crosstalk occurs between cell cycle transition regulators and metabolism regulators (4, 6). The study by Colombo et al. (5) demonstrates that the levels of two enzymes, PFKFB3 (6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase, isoform 3) and GLS1 (glutaminase 1), which play key roles in the glycolysis and glutaminolysis pathways, respectively, are controlled by two ubiquitin ligase complexes: APC/C<sub>Cdh1</sub> and SCF<sub>βTrCP</sub>. APC/C<sub>Cdh1</sub> mediates the degradation of both PFKFB3 and GLS1 as cells exit mitosis and during the G1 phase, whereas SCF<sub>βTrCP</sub> specifically targets PFKFB3 during S phase. The oscillation in protein levels of these two enzymes coincides with their respective metabolic activities, in terms of lactic acid production and glutamine uptake (Fig. 1A). Experiments coupling siRNA knockdowns and cell cycle synchronization further reveal that depletion of either PFKFB3 or GLS1 interferes with the G1/S transition, whereas only GLS1, but not PFKFB3, is required to complete S phase. This study (5), together with previous findings by Moncada and coworkers (7–9), suggests that the metabolism of glucose and glutamine is tightly controlled at distinct phases of the cell cycle through the activity of APC/C<sub>Cdh1</sub> and SCF<sub>βTrCP</sub> (Fig. 1B).

APC/C<sub>Cdh1</sub> and SCF<sub>βTrCP</sub> are known to be major regulators of cell cycle progression (10, 11). However, accumulating evidence now suggests additional roles in regulating cell metabolism. Colombo et al. (5) report that the decrease in APC/C<sub>Cdh1</sub> activity that occurs in late G1 leads to the accumulation of PFKFB3 and GLS1, and, consequently, elevated glycolysis and glutaminolysis. This observation supports their previous finding that overexpression of Cdh1 largely prevents the increase in glycolysis and reduces the proportion of cells in S phase (7). APC/C<sub>Cdh1</sub> is active during late anaphase, telophase, and G1, and it is an important contributor to G1 maintenance by promoting the degradation of many positive regulators of cell proliferation (10, 11). Inactivation of APC/C<sub>Cdh1</sub> in late G1 is required for cells to efficiently proceed into S phase and divide (10, 11). The study by Colombo et al. (5) suggests that the inactivation of APC/C<sub>Cdh1</sub> also plays a role in satisfying metabolic needs during the G1/S transition.

Interestingly, the authors also found that SCF<sub>βTrCP</sub> is responsible for PFKFB3 degradation and decreased glycolysis activity in S phase. This scenario is reminiscent of the “dual mode” regulation of other proteins (including CDC25A and Claspin) by APC/C<sub>Cdh1</sub> and SCF<sub>βTrCP</sub>, the former targeting them in G1 and the latter in other phases (CDC25A in S phase and Claspin in G2) (12, 13). Notably, SCF<sub>βTrCP</sub> has been implicated in regulating other pathways that control cellular metabolism. DEPTOR is a recently identified SCF<sub>βTrCP</sub> substrate that directly regulates the activity of mammalian target of rapamycin kinase (mTOR), a key player in cell growth and metabolism (14–17). By mediating the degradation of DEPTOR, SCF<sub>βTrCP</sub> enhances mTOR activity and responds to nutrient stimuli, such as glucose or serum (15–17).

Degradation via SCF ligases often requires posttranslational modifications of the substrates (12), and Colombo et al. now show that phosphorylation of PFKFB3 on Ser273, which is present in a conserved SCF<sub>βTrCP</sub> recognition motif (2086ĐGSxS<sub>273</sub>), is required for degradation (5). However, the kinase(s) responsible for this modification and, presumably, for the second serine in the degradation motif (Ser269), remain(s) unknown. It is also noteworthy that the levels of PFKFB3 and GLS1 are already low in G2 phase, when APC/C<sub>Cdh1</sub> is still inactive, suggesting the involvement of additional regulatory mechanisms. Further investigation of the signaling pathways controlling the levels of PFKFB3 and GLS1 will provide deeper insight into this cell cycle-dependent degradation.

Significantly, APC/C<sub>Cdh1</sub> is also active in postmitotic cells (10) and, in fact, PFKFB3 was originally reported to be targeted by APC/C<sub>Cdh1</sub> in neurons (18). Attenua-
tion of glycolysis in these terminally differentiated cells appears to prevent oxidative stress and apoptosis caused by glucose oxidation. It would be interesting to understand whether GLS1 is also down-regulated in postmitotic cells.

The accelerated utilization of glucose and glutamine in cancer cells goes beyond the need for energy. This metabolic reprogramming also contributes to the rapid production of biosynthetic precursors, such as nucleotides, carbohydrates, amino acids, and fatty acids, which are required for cell proliferation (19). To maximize the rate of anabolic growth, the individual pathways controlling glycolysis, gluconeogenesis, oxidative phosphorylation, and the pentose phosphate pathway, as well as others, must be interconnected and temporally controlled. The study by Colombo and colleagues shows that PFKFB3 levels and, consequently, glycolysis, are elevated in mid- to late G1 and decrease during S phase. One possible explanation for this behavior is that, by switching off the glycolysis pathway, glucose is diverted into the pentose phosphate pathway and converted to ribose-5-phosphate for nucleotide synthesis. Alternatively, it may be used to provide carbons for fatty acid synthesis. Unlike glucose, glutamine is required for the G1/S transition and throughout S phase (5). These observations suggest different roles for the metabolic pathways at distinct phases of the cell cycle. It will be interesting to determine whether nonmalignant cells also use these mechanisms to regulate energy production and macromolecular precursor biosynthesis.

An emerging theme in cancer is that oncogenic gene alterations reprogram the metabolic network, thus enabling tumorigenesis (20). Cdh1 displays tumor suppressor activity, as supported by its down-regulation or the inactivation of APC/C[Cdh1] observed in human cancers (10, 13). It will be worthwhile to test if deregulation or mutations of Cdh1 or certain substrates contributes to alterations in cell metabolism pathways, leading to malignant transformation of the cells.

Overall, this study (5) sheds light on how metabolic pathways, such as glycolysis and glutaminolysis, are linked to cell cycle progression. Given their timely and selective targeting of substrates, APC/C[Cdh1] and SCF[TrCP] coordinate global metabolism networks with the cell cycle. Further investigation will provide important information about the contribution of metabolic pathways to cell growth and malignancy, as well as the specific metabolic features coopted by tumor cells.