ABSTRACT

"Connecting cell cycle progression to metabolic requirements"

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Cell proliferation is accompanied by an increase in the utilization of glucose and glutamine. The proliferative response is dependent on a decrease in the activity of the ubiquitin ligase anaphase-promoting complex/cyclosome (APC/C)-Cdh1 which controls G1- to-S-phase transition by targeting degradation motifs, including the KEN box. This occurs not only in cell cycle proteins but also in the glycolysis-promoting enzyme 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase isoform 3 (PFKFB3), as we have demonstrated in cells in culture as well as in proliferating human T lymphocytes. Moreover, we have found that glutaminase 1 is a substrate for this ubiquitin ligase and appears at the same time as PFKFB3 in proliferating cells. Glutaminase 1 is the first enzyme in glutaminolysis and converts glutamine to glutamate, yielding intermediates for cell proliferation. Thus APC/C-Cdh1 is responsible for the increased utilization not only of glucose but also of glutamine and, as such, accounts for the critical step that links the cell cycle with the metabolic substrates essential for its progression. A further degree of control is provided by a second ubiquitin ligase – SCF (Skp1/CUL-1/F-box protein)-□-TrCP – which causes the disappearance of PFKFB3 during late G1/S. Thus the presence of PFKFB3 is tightly controlled to ensure the upregulation of glycolysis at a specific point in G1. The relevance of these observations to understanding of the proliferative and metabolic changes that occur in normal and in cancer cells will be discussed.