DAPk and pyruvate kinase
Unlikely partners in cancer metabolic regulation

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Death Associated Protein kinase (DAPk) is classically known for its role in several cell death promoting pathways, in which it usually functions through phosphorylation of various protein substrates. Its role in induction of apoptosis, programmed necrosis and autophagic cell death can, at least in part, explain its tumor suppressor activity.5,6 Indeed, silencing of DAPk expression through promoter hypermethylation has been described in many cancers rising from a wide range of tissue types.2,3 Earlier this year, we reported a new function for DAPk in which it exerts its anti-proliferative function not by inducing cell death, nor by phosphorylation of a downstream protein.4 We identified the glycolytic enzyme pyruvate kinase as a binding partner of DAPk and have demonstrated that this interaction leads to an increase in pyruvate kinase activity in a manner independent of DAPk phosphorylation. Pyruvate kinase is a key enzyme in glycolysis and as such is highly important for tumor cell metabolism. Changes in the metabolic profile of cells following cancerous transformation have been known for decades.5 Cancer cells rely heavily on glycolysis and accordingly, glucose uptake and lactate secretion are characteristically increased in these cells. Cancer cells often display expression of the embryonic isoform (M2) of pyruvate kinase, which is normally switched off during cell differentiation.6 Interestingly, this isoform has lower baseline activity compared with the isoforms normally found in adult cells, and requires allosteric activation by Fructose-1,6-bisphosphate, an earlier glycolytic intermediate, for full physiological activity.6 While this seems counter-intuitive, the ability of this enzyme to be regulated may be of particular importance for cancer cells. Slowing down glycolytic flux allows glycolytic intermediates to build up and be diverted to other metabolic pathways, where they serve as substrates for synthesis of amino acids and nucleotides that are required as building blocks for the proliferating cancer cells.7

Pyruvate kinase activation by DAPk is interesting for both sides of this partnership. For pyruvate kinase, this regulation is significant in that DAPk is to date, its only known activator protein. Furthermore, the mode of activation is mechanistically different than that induced by Fructose-1,6-bisphosphate. From the point of view of DAPk, pyruvate kinase is different from other protein partners in two aspects. First, it is not a phosphorylation substrate. Interestingly, a few kinase-independent functions have already been described for DAPk. For example, upon direct binding DAPk can activate MARK1/2, which phosphorylate tau and MAPs, thereby affecting microtubule assembly dynamics.8 Second, by activating pyruvate kinase, DAPk should impede cell proliferation rather than induce cell death. This was indeed found to be the case as cells overexpressing the kinase “dead” DAPk variant displayed a reduced proliferation rate. By modulating glycolytic flux, DAPk’s function as a metabolic regulator is independent of any of its previously described cell-death promoting affects.

While the anti-proliferative functionality of DAPk would support its tumor-suppressive activity, practically, it would be hard to discriminate this from its cell-death inducing function. However, circumstances could arise where these two facets of DAPk’s function are uncoupled. Namely, we speculate that in some instances, DAPk’s metabolic function would be beneficial to certain cancers, providing that its cell death inducing functions are circumvented. If this is true, we would expect to find examples of elevated DAPk expression concomitant with attenuated catalytic activity. Notably, there are several examples in the literature of cancers and virally transformed cells where both conditions have been met.5,9-11 These examples support the possibility that DAPk has a dual function in tumor suppression by inducing cell death and independently slowing down cell proliferation through activation of pyruvate kinase. Further study on the metabolic profile of the cancers in which DAPk expression is maintained could possibly explain the selective advantage of DAPk upregulation.

New insights have recently been achieved on the regulation of DAPk activity, demonstrating that inhibitory autophosphorylation is regulated by a newly identified GTPase domain.12 That DAPk can function through direct protein-protein interaction without the need for release of autoinhibitory phosphorylation and catalytic activity suggests that different mechanism(s) are involved in the regulation of its metabolic function. Our results demonstrate that sub-cellular localization of pyruvate kinase has a part as DAPk/pyruvate kinase complexes were localized to the cytoskeleton.8 Identifying the mechanisms that control DAPk’s metabolic function would offer new insight.
into the ways DAPk can affect cellular proliferation and death, and their role in tumor progression. Moreover, its newly identified function as a metabolic regulator suggests DAPk as a potential integration hub that brings together metabolic and cell death signaling.

References