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Taking aim at glycolysis with CDK8 inhibitors

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Abstract

Dependence on glycolysis in aerobic conditions, a frequent metabolic derangement in cancer cells, suggests a therapeutic opportunity. Now, through chemical genetics, CDK8, a kinase associated with the Mediator transcriptional co-activator complex, has emerged as an upstream inducer of glycolysis and a possible target for anti-cancer drug discovery.

Keywords

Cancer; CDK8; Mediator; chemical genetics; transcription; glycolysis

Derangement of cellular metabolism is a hallmark of cancer. A classical example is the increased reliance of tumor cells on glycolysis under aerobic conditions, known as the Warburg effect. Underlying this phenomenon is the increased expression of glycolytic-pathway genes, normally induced by low oxygen concentration, under normoxic conditions. The presumed driver of this dysregulation is the adaptation to transient hypoxia as tumor cells outgrow their blood supply. Increased dependency of cancer cells on anaerobic metabolism might confer vulnerability to drugs that disrupt glycolysis, either directly or indirectly [1].

But which pathways might be targeted to block growth or promote death of tumor cells without causing unacceptable toxicity in normal tissues? The elucidation of gene expression programs that are normally activated in response to hypoxia and derepressed in tumor cells under normoxic conditions raises the possibility of more surgical approaches to target altered metabolism in human cancers. In particular, the hypoxia-inducible factors (HIFs)—a family of DNA-binding transcriptional activators—have been implicated in the regulation of glycolytic-pathway genes. One subunit of these heterodimeric factors is hydroxylated under normoxic conditions and thereby targeted for ubiquitin-dependent degradation, but becomes stabilized in hypoxia, leading to activation of HIF target genes. Alternative pathways of HIF stabilization are activated in certain tumor cells and are thought to contribute to “aerobic glycolysis” [2].

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The HIFs themselves might be potential drug targets. In addition to the usual difficulties in targeting transcription factors without enzymatic functions, however, the HIFs pose special challenges to any direct, small molecule-based approach. In different contexts, activity of a given HIF can be oncogenic or tumor-suppressive. Moreover, the two major HIF isoforms, containing either the HIF1 α or HIF2 α oxygen-sensing subunit, can exert opposite effects on target gene expression, cell signaling pathways and survival [2].

HIF1A (containing HIF1 α) is overexpressed in certain cancers, and requires the co-activator function of the Mediator complex [3], which transduces signals between transcriptional activators bound to cognate response elements and the promoter-bound, RNA polymerase II (Pol II)-containing preinitiation complex (PIC) (Figure 1) [4]. The specific form of Mediator that cooperates with HIF1A contains the CDK8 module—a four-subunit assembly consisting of the CDK8 catalytic subunit, activating cyclin C subunit and two accessory proteins, MED12 and MED13. The CDK8 complex is dissociable from the core Mediator, which can alternatively bind a distinct module containing CDK19 as its catalytic subunit. The mutual exclusivity of CDK8 and CDK19 provides additional gene specificity to the Mediator-associated kinase activity, which can be either repressive or activating at different promoters. Depletion of CDK8, but not of CDK19, specifically blocked induction of HIF1A target genes in response to hypoxia in human colorectal cancer-derived HCT116 cells [3], suggesting CDK8 as a pharmacological target through which to leverage the possible addiction of tumor cells to HIF-driven transcription.

Espinosa and colleagues have now strengthened the case for CDK8 as a potential drug target in human cancers [5]. Following up their previous work, these investigators established a cell-based system in which CDK8 could be inhibited without affecting its closely related paralog, CDK19. To do so, they replaced wild-type CDK8 in HCT116 cells with an analog-sensitive (AS) variant, in which the ATP-binding site is expanded by changing a conserved bulky residue (the “gatekeeper”) to a glycine residue [6]—a strategy previously applied to other CDKs in the human transcription machinery [7–9]. The CDK8^{F97G} (CDK8^{as}) variant was sensitive to a bulky adenine analog that did not inhibit wild-type CDK8. The mutant was also hypomorphic; *CDK8^{as/as}* cells grew more slowly than parental, wild-type cells, and had defects in glycolytic-pathway gene expression and glucose metabolism even in the absence of the inhibitor (although its presence tended to strengthen the phenotypic effects).

The effects of CDK8 impairment included slowed growth in monolayer or three-dimensional culture, impaired anchorage-independence, reduced clonogenic efficiency and decreased growth rate of *CDK8^{as/as}* xenograft tumors in nude mice. Compared to wild-type HCT116 cells, *CDK8^{as/as}* cells had constitutive reductions in glucose uptake and extracellular acidification rate (a measure of glycolytic activity), which were exacerbated by hypoxia. This led the authors to ask if the mutant cells were hypersensitive to an inhibitor of glycolysis, 2-deoxy-D-glucose (2DG). Indeed, they were, and this 2DG hypersensitivity could be phenocopied in diverse, wild-type tumor cells by treatment with Senexin A, an inhibitor of both CDK8 and CDK19.

Might the CDK8-Mediator be an Achilles’ heel, i.e., a pharmacologic target through which to impede glycolysis in vulnerable tumor cells? Some cautions and caveats are probably

warranted. Although CDK8 occupancy measured by ChIP-seq is relatively high at hypoxia-inducible genes generally, and at HIF1A targets specifically, it is not restricted to those loci [3], and previous studies with CDK8/19 inhibitors suggest more widespread effects on transcription—both positive and negative—when Mediator-associated kinases are inhibited. This raises a concern that a potent CDK8/19 inhibitor might critically disrupt gene expression in normal tissues. Recently, however, a different CDK8/19 inhibitor, Cortistatin A, was shown to have anti-leukemic efficacy [10]; the proposed mechanism of action was through up-regulation of genes controlled by specialized transcriptional response elements called superenhancers (SEs)—paradoxically, the same subset of genes *repressed* by a bromodomain protein BRD4 inhibitor, which also promoted death of leukemic cells. Moreover, inhibitors of a different transcriptional CDK—CDK7, associated with general transcription initiation factor (TF) IIH—are cytotoxic towards select tumor cells [11]. CDK7 activity is thought to be required for transcription of many or most protein-coding genes in eukaryotic cells; the basis for its selective anti-cancer efficacy appears to be the heightened dependency of certain tumors on SE-driven gene expression programs.

Whether the increased sensitivity of HIF1A targets to CDK8 inhibitors will provide a similar therapeutic window remains to be tested. Potentially complicating the picture, it will be difficult, at best, to inhibit CDK8 selectively without also inhibiting CDK19; the two kinases are >90% identical. The isoform-specificity achieved by the chemical-genetic approach is therefore unlikely to be recapitulated through chemistry alone. On the other hand, it might not need to be, given the synthetic lethality achieved by combining treatments with Senexin A and 2DG [5]. Recently, a similar, synergistic cell killing effect was described for CDK7 inhibitors in combination with p53-activating drugs in tumors that were not intrinsically hypersensitive to the inhibitors as single agents [12]. Therefore, CDK inhibitors might have broader utility as anticancer drugs in rational combinations with agents that make tumor cells—but not normal cells—vulnerable to perturbation of the transcriptional machinery.

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Figure 1. CDK8, a druggable target in aerobic glycolysis?

Expression of glycolytic-pathway genes depends on the co-activator function of CDK8-Mediator, which transmits transcription-stimulatory signals from hypoxia-inducible factor 1A (HIF1A), bound at its response element (RE), to the promoter-bound, Pol II-containing pre-initiation complex (PIC). This pathway of transcriptional activation is normally triggered by hypoxia but becomes constitutively active in cancer cells, potentially sensitizing them to small-molecule inhibition of CDK8, the only known enzymatic function within the CDK8-Mediator complex.