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Metabolites, genome organization, and cellular differentiation gene programs

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The nutrient environment and metabolism play a dynamic role in cellular differentiation and research is elucidating the mechanisms that contribute to this process. Metabolites serve as an effective bridge that helps to translate information about nutrient states into specific interpretations of the genome. Part of this activity relates to the role for metabolites in regulating epigenetic processes as well as a newly appreciated role for metabolites in the regulation of genome organization. In this review, we will highlight recent research that has defined roles for metabolism in the organization and interpretation of the genome and how this influences cellular differentiation decisions. We will integrate information about how nutrients, such as glutamine, regulate metabolites, such as alpha-ketoglutarate, and highlight how these pathways influence epigenetic states as well as CTCF association and genome organization. We will also discuss mechanistic similarities and differences between normal differentiation states associated with embryonic stem (ES) cells and T cells and how this might relate to dysregulated states such as those associated with tumor infiltrating lymphocytes.

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Metabolism is now appreciated to be a central component of cellular differentiation. Studies in embryonic stem (ES) cells have led the way in defining how nutrient intake initiates changes in the accumulation of metabolites [1••,2–5]. These studies have also uncovered roles for metabolites in regulating cellular differentiation programs in part through their ability to act as donors, substrates and cofactors for epigenetic modifications and epigenetic-modifying complexes [6,7]. Research in numerous developmental systems, including in the immune system, have extended these results to indicate that the mechanistic events that occur in ES cells are conserved in diverse cellular settings [8,9,10••]. Taken together, the current state of the field indicates a striking conservation of the mechanisms that translate information about the nutrient environment into gene expression programs.

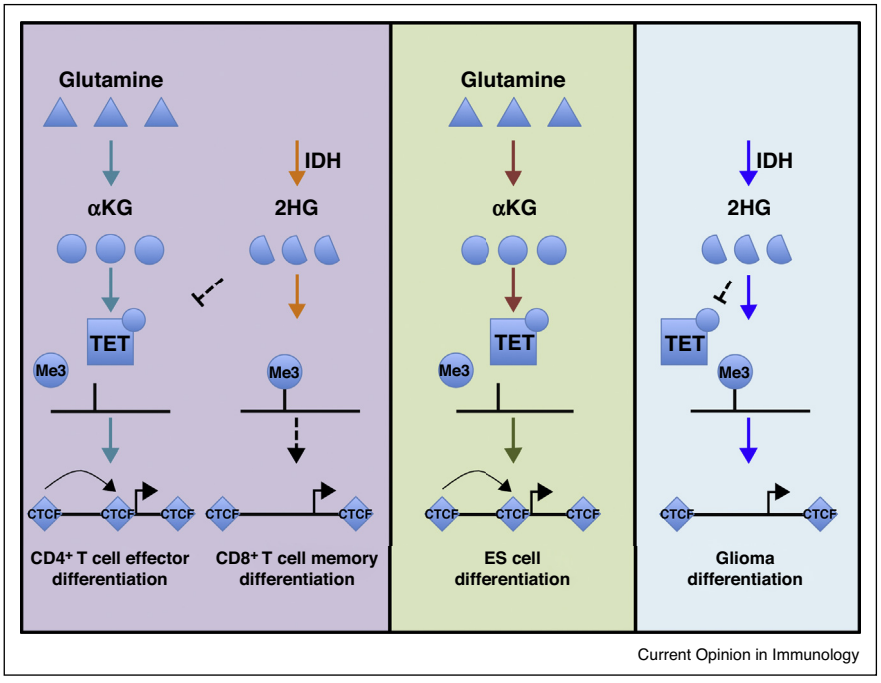
DNA methylation influences CTCF association and genome organization in cellular differentiation

DNA methylation plays an important role in regulating both normal development and pathogenic states [11–13]. For instance, in T cell differentiation, DNA methylation states are important for promoting the balance between the effector and memory program, with dysregulated DNA methylation leading to an exhausted state [14–16]. Intriguingly, DNA methylation has also been shown to play an important role for CCCTC-binding factor (CTCF) association and genome organization in several cellular settings [17–19]. In B cells and early T cell development, the expression of enhancer RNAs (eRNAs) or long noncoding RNAs (lncRNAs) can cause hypomethylation of DNA regions that promotes CTCF association and changes in genome topology [20,21••]. It is now appreciated that the microenvironment can influence DNA methylation states through regulating the balance of DNA methyltransferase and DNA demethylase activities. The nutrient environment plays a role in this process by regulating the accumulation of metabolites such as S-adenosylmethionine (SAM), the donor for DNA methyltransferases, alpha-ketoglutarate (αKG), a required cofactor for DNA demethylases, and 2-hydroxyglutarate (2HG), a competitive inhibitor of αKG in DNA-demethylase activity [6,22,23]. Thus, it is possible in conditions where the nutrient environment or metabolites regulate the state of DNA methylation, this could provide a mechanistic link between metabolism, epigenetics, and genome organization events.

Metabolites αKG and 2HG influence DNA methylation, CTCF association and genome topology

The interplay between metabolism, DNA methylation and genome organization is an emerging area of interest in defining the mechanistic connections between metabolism and cellular differentiation. Recent conceptual advances in both normal and pathogenic differentiation states have identified roles for metabolic events in the regulation of CTCF association with the genome, which

Figure 1



Mechanistic connections between metabolites, epigenetics, CTCF association and genome organization events. Shown is a schematic representation of the concepts presented in the review related to how metabolites impact CTCF association and genome organization in T cells (purple), ES cells (green), and glioma cells (blue). In the ES cell panel, different colored arrows represent the findings from multiple independent studies. The solid arrows indicate mechanistic interpretations with at least some supporting experimental evidence whereas the dashed arrows/lines indicate speculative interpretations of mechanistic steps based upon the integration of data from other cellular settings.

in turn, regulates genome topology [10••,24••]. For example, the dysregulated metabolic state in gliomas with mutations in the isocitrate dehydrogenase (IDH) enzyme disrupts CTCF association and genomic interactions surrounding the *PDGFRA* oncogene [24••]. Mechanistically, mutations in IDH can cause the overproduction of the metabolite 2HG. 2HG is a competitive inhibitor of αKG, with αKG serving as a required cofactor for both histone and DNA demethylase complexes [25,26]. DNA methylation has been shown to prevent CTCF association with a subset of sites in a mechanism that contributes to the regulation of genomic organization in a cell-type specific manner [19,27,28]. The IDH-mutation-sensitive CTCF binding events observed in glioma cells are potentially related to changes in DNA methylation because enhanced methylation at select CTCF sites correlates with diminished CTCF association (Figure 1) [24••]. These data suggest that dysregulated metabolic states that influence DNA methylation can play a role in CTCF association, genomic organization and pathogenic gene programming states.

Connections between natural metabolic states, DNA methylation, CTCF association, and genome organization have been found within the context of the IL-2-sensitive differentiation program in CD4$^+$ T cells [10••]. In CD4$^+$ T helper type 1 (Th1) cells, the IL-2-sensitive program is regulated by both glutamine- and αKG-sensitive events. Importantly, IL-2- and αKG-sensitive events promote CTCF association with select sites in the genome and this correlates with changes in genomic organization [10••]. Similar to the mechanistic interpretations from the pathogenic state of glioma cells, it appears that at least some of the αKG-sensitive CTCF association in the context of normal T cell differentiation is regulated by changes in DNA methylation. Specifically, the IL-2- and αKG-sensitive reduction in DNA methylation surrounding loci such as *Sell* (encodes CD62L) in primary CD4$^+$ Th1 cells correlates with enhanced CTCF association [10••]. The DNA methylation status at the *Sell* promoter is also impacted by 2HG accumulation in the context of CD8$^+$ T cell differentiation, with enhanced DNA methylation correlating with the accumulation of 2HG [9]. Thus, the metabolites αKG and 2HG reciprocally control the state of DNA methylation at the *Sell* promoter during normal T cell differentiation, and interestingly, the region of differential methylation overlaps with an IL-2- and αKG-sensitive CTCF site [9,10••]. Together, these data indicate that the balance between the metabolites αKG and 2HG impacts normal T cell differentiation programming, while the data from