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Review

Metabolic interactions with cancer epigenetics

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ABSTRACT

Cancer cells have epigenetic alterations that are known to drive cancer progression. The reversibility of the epigenetic posttranslational modifications on chromatin and DNA renders targeting these modifications an attractive means for cancer therapy. Cellular epigenetic status interacts with cell metabolism, and we are now beginning to understand the nature of how this interaction occurs and the biological contexts that mediate its function. Given the tremendous interest in understanding and targeting metabolic reprogramming in cancer, this nexus also provides opportunities for exploring the liabilities of cancers. This review summarizes recent developments in our understanding of the interaction of cancer metabolism and epigenetics.

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1. Introduction

The term epigenetics has been used to describe heritable alterations of cellular phenotypes independent of mutations in the DNA sequence (Morgan et al., 2005). Now,it is also commonly referred to as a state of chromatin and DNA involving specific posttranslational modification of histones such as acetylation, methylation, ubiquitination, phosphorylation, crotonylation, and methylation, along with other modifications to DNA and RNA that affect gene expression (Dawson and Kouzarides, 2012; Tan et al., 2011). Changes in the epigenetic landscape have become evident in many pathophysiological conditions including cancer and diabetes (Baylin and Jones, 2011; Feinberg and Tycko, 2004; Suva et al., 2013). Cancer epigenetics was characterized in 1983 (Feinberg and Vogelstein, 1983; Gama-Sosa et al., 1983), when specific DNA methylation patterns of genes were found in human tumors in comparison to their normal tissue counterparts. It is now widely considered a significant contributor to cancer initiation and progression, along with genomic mutations (Sharma et al., 2010; Shen and Laird, 2013; Suva et al., 2013). In contrast to irreversible genetic

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mutations, the reversible property of epigenetic modifications along with the enzymatic nature of these modifications allows for therapeutic targeting through possible reversion of the epigenetic state associated with these modifications (Mosammaparast and Shi, 2010). To our knowledge, multiple drugs targeting epigeneticmachinery have been approved by the Food and Drug Administration, in addition to a large variety of investigational compounds that are currently under avid clinical and laboratory investigation (Johnson et al., 2015; Yun et al., 2012). Despite advances in our understanding of cancer epigenetics over the past twenty years, what directly determines epigenetic status remains largely elusive. Recently, it has been proposed that metabolism interacts with epigenetic machinery (Carrer and Wellen, 2015; Gut and Verdin, 2013; Kaelin and McKnight, 2013) and that this interaction may have a substantial role in determining epigenetic state. Thus, there is an intriguing link between metabolism and epigenetics in cancer.

Metabolic reprogramming is a hallmark of cancer (Hanahan and Weinberg, 2011) with several common themes within this program that have emerged (Pavlova and Thompson, 2016). Now, cumulative evidence has reinforced this observation and revealed many additional metabolic characteristics in cancer cells, including alterations in the metabolism of glucose, amino acids, nucleotides and lipids (Boroughs and DeBerardinis, 2015; Pavlova and Thompson, 2016; Ward and Thompson, 2012). Furthermore, these metabolic features are heterogeneous and each cancer cell likely exhibits different metabolic features depending on its genetic, epigenetic, and environmental state.

In this review, we discuss the connection between cancer metabolism and epigenetics. We discuss metabolic pathways that can affect cellular epigenetics. We then highlight recent work on the interaction of metabolism and epigenetic modifications, focusing on methylation of DNA and histones, and acetylation of histones. In the end, we discuss the therapeutic potential of simultaneously targeting these connected processes. While this discussion due to space constraints is not comprehensive, it is our hope that it will give the reader an introduction to the key metabolic pathways known to affect epigenetics.

2. Serine, glycine, and one-carbon metabolism

3-Phosphoglycerate dehydrogenase (*PHGDH*) encodes the enzyme that diverts glycolysis for serine synthesis. Quantitative characterizations of serine synthesis and the discovery of amplifications in *PHGDH* have reignited considerable interest in understanding the metabolic network downstream of this enzyme. This network, collectively referred to as serine, glycine, and one-carbon (SGOC) metabolism (Fig. 1), encompasses a complex metabolic network involving the interconnected folate and methionine cycles (Locasale, 2013). In fact, modern cancer therapy partially arises from antagonizing folate metabolism that has been used in practice for over 60 years (Farber and Diamond, 1948; Locasale, 2013). SGOC metabolism integrates various nutrient inputs such as vitamins, glucose and amino acids, and generates substrates for the synthesis

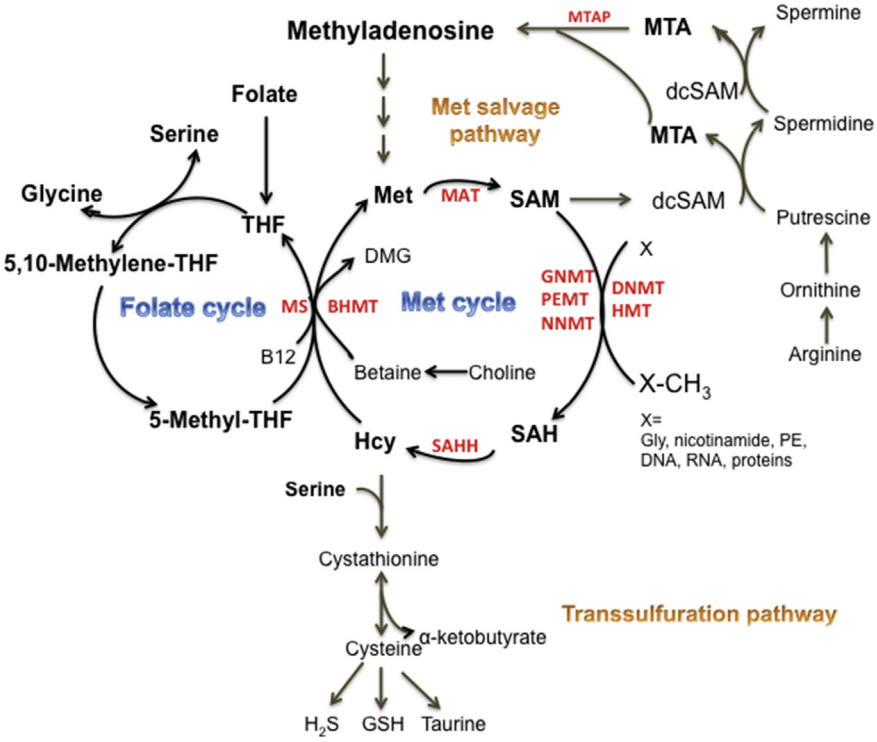

Fig. 1. One-carbon metabolism. One-carbon metabolism is encompassed of a complex metabolic network centered by the folate and methionine cycles. Serine and glycine provide one-carbon unit to the folate cycle. The folate cycle is coupled with the methionine (Met) cycle for Met regeneration catalyzed by methionine synthase (MS). Met can also be regenerated through betaine-homocysteine (Hcy) methyltransferase (BHMT) using betaine as the one-carbon donor. Met provides the essential substrate for MATs (methionine *S*-adenosyltransferases), generating *S*-adenosylmethionine (SAM). SAM methylates a wide range of substrates DNA, RNA, lipids and proteins including histones, and generating *S*-adenosylhomocysteine (SAH). SAH is catalyzed by SAH hydrolase to Hcy. One-carbon metabolism also interacts with the transsulfuration pathway and the methionine salvage pathway that is coupled with the polyamine synthesis. In the transsulfuration pathway, serine is required to divert Hcy for synthesis of cystathionine, and cystathionine is then catabolized into cysteine, the limiting factor for glutathione (GSH) production. Cysteine also provides substrate for the production of taurine and hydrogen sulfide (H_2S). In the Met salvage pathway, SAM is decarboxylated to provide the supplaminopropyl groups to putrescine, supporting the polyamine synthesis. The byproduct 5′-methylthioadenosine (MTA) is salvaged back for SAM generation, with the initial step is catalyzed by MTA phosphorylase (MTAP). Other abbreviations: DNMT, DNA methyltransferase; HMT, histone methyltransferase; GNMT, glycine *N*-methyltransferase; PEMT, phosphatidylethanolamine *N*-methyltransferase; NNMT, nicotinamide *N*-methyltransferase.