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Epithelial–mesenchymal transition in human cancer: Comprehensive reprogramming of metabolism, epigenetics, and differentiation

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ABSTRACT

The epithelial–mesenchymal transition (EMT) is a developmental process that is important for embryogenesis, wound healing, organ fibrosis, and cancer metastasis. Cancer-associated EMT is not a simple process to acquire migration and invasion ability, but a complicated and comprehensive reprogramming, involved in metabolism, epigenetics and differentiation, through which differentiated epithelial cancer cells reverse to an undifferentiated state, not only expressing stem cell markers, but also acquiring stem cell-like functions. Here we review recent ideas and discoveries that illustrate the links among metabolism, epigenetics, and dedifferentiation during EMT, with special emphasis on the primary driving force and ultimate goal of cancer-associated EMT — of the energy and for the energy. Furthermore, we highlight on the specificity of epigenetic modification during EMT, with an aim to explain how the repression of epithelial genes and activation of mesenchymal genes are coordinated simultaneously through EMT. Finally, we provide an outlook on anti-EMT therapeutic approach on epigenetic and metabolic levels, and discuss its potential for clinical application.

Contents

Abbreviations: 2HG, 2-hydroxyglutarate; α-KG, α-ketoglutarate; βOHB, β-hydroxybutyrate; ACL, ATP-citrate lyase; AML, acute myeloid leukemia; BLBC, basal-like breast cancer; CAFs, cancer-associated fibroblasts; CSCs, cancer stem cells; DNMTs, DNA methyltransferases; EMT, epithelial–mesenchymal transition; EMT-TFs, epithelial–mesenchymal transition transcriptional factors; ESCs, embryonic stem cells; Floate 1C pool, floate one-carbon pool; EZH2, enhancer of zeste homolog 2; FAD, flavin adenine dinucleotide; FBP1, fructose-1,6-biphosphatase; FH, fumarate hydratase; G-6-P, glucose-6-phosphate; GLUT1/3, glucose transporters 1/3; GSH, glutathione; GSSG, oxidized glutathione; H3K4me2/3, histone H3 lysine 4 dimethylation/trimethylation; H3K9Ac, histone H3 lysine 9 acetylation; HAT, histone acetyl transferase; HDAC, histone deacetylase; HIF-1, hypoxia-inducible factor 1; HMTs, histone methyltransferases; HSC, hematopoietic stem cell; iPSCs, induced pluripotent stem cells; IDH, isocitrate dehydrogenase; JHDMs, Jumonji C domain-containing histone lysine demethylases; LOCKs, large organized heterochromatin K9-modifications; LDH, lactate dehydrogenase; LSD1, lysine-specific demethylase-1; MAT, methionine adenosyl transferase; MDS, myelodysplastic syndrome; NAD, nicotinamide adenine dinucleotide; NADP, nicotinamide adenine dinucleotide phosphate; O-GlcNAc, O-linked N-acetylglucosamine; OxPhos, oxidative phosphorylation; PDK1, pyruvate dehydrogenase kinase 1; PFK1, phosphofructose kinase 1; PPP, pentose phosphate pathway; ROS, reactive oxygen species; SAH, S-adenosyl homocysteine; SAM, S-adenosyl-methionine; SDH, succinate dehydrogenase; TCA cycle, tricarboxylic acid cycle; TET, ten eleven translocation; Thr, threonine.

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1. Introduction

The ability of epithelial cells to undergo mesenchymal transitions during embryogenesis, wound healing and malignant tumor progression is now widely accepted as a core biological process termed the epithelial–mesenchymal transition (EMT) (Yang & Weinberg, 2008; Kalluri & Weinberg, 2009; Polyak & Weinberg, 2009; Thiery et al., 2009). In order to invade and metastasize, tumor cells shed their differentiated epithelial characteristics, including cell–cell adhesion and polarity, and acquire mesenchymal traits, such as motility, invasiveness and, importantly, many of the attributes of stem cells (Mani et al., 2008; Morel et al., 2008; Polyak & Weinberg, 2009; Thiery et al., 2009; Chaffer et al., 2011; Gupta et al., 2011; Chaffer et al., 2013; Tam & Weinberg, 2013) (Fig. 1). It is of central importance that EMT processes are reversible, so that mesenchymal cells can undergo mesenchymal–epithelial transition (MET) to differentiate back to epithelial phenotypes (Yang & Weinberg, 2008; Kalluri & Weinberg, 2009; Thiery et al., 2009). This reverse transition plays a key role in the formation of macroscopic metastases in different organs (Yang et al., 2011; Yao et al., 2011; Gunasinghe et al., 2012). Therefore, EMT is likely sustained by transient molecular changes induced by extracellular cues from the tumor microenvironment, hypoxia for example, and not by permanent genetic alterations. Indeed, it is becoming increasingly evident that the reversible nature of EMT is closely associated with reversible epigenetic regulatory mechanisms, which refers to a series of stable but reversible modifications, not directly affecting the DNA primary sequence, but rather relies on dynamic transcriptional programming effects (Wu et al., 2012; Kiesslich et al., 2013; Tam & Weinberg, 2013). Such heritable regulations in the pattern of gene expression are mediated by the DNA methylation of CpG dinucleotides and several post-transcriptional covalent modifications of the NH2 terminal of histone proteins, including acetylation, methylation, biotinylation, and phosphorylation (Kiesslich et al., 2013). Since most enzymes responsible for adding or removing epigenetic modifications require substrates or cofactors that are intermediate metabolites of cells and capable of diffusing through nuclear pores, such as acetyl-CoA, NAD^+, SAM, α-KG, and FAD (Lu & Thompson, 2012; Kaelin & McKnight, 2013), it is not difficult to imagine that the fluctuation of the levels of metabolites could modulate the activities of chromatin-modifying enzymes, influence chromatin dynamics, and therefore deliver metabolic information to nuclear transcription. Recent evidence has confirmed that the availability of the necessary metabolites affects epigenetic modifications, providing a direct link between nutritional changes, metabolic output, and gene expression (Lu & Thompson, 2012; Kaelin & McKnight, 2013; Shankar et al., 2013). Consequently, it is likely that abnormal microenvironmental conditions such as hypoxia, low pH, or nutrient deprivation elicit a series of responses in tumor cells, including metabolic adaptation, epigenetic alteration, as well as EMT-associated dedifferentiation. This would ultimately result in metastasis to distant tissues and organs that can provide the requisite nutrients to support the fast growth. Here we review recent ideas and discoveries that illustrate the links among metabolism, epigenetics, and dedifferentiation during EMT, and provide an outlook on anti-cancer therapeutic approaches that target epigenetic and metabolic programs.

2. Metabolic reprogramming during epithelial–mesenchymal transition: maintaining an undifferentiated state by enhancing glycolysis

EMT is characterized by reversible changes in cell type with the acquisition of both stem cell and malignant traits (Morel et al., 2008; Polyak & Weinberg, 2009; Thiery et al., 2009; Tam & Weinberg, 2013). Traditionally, CSCs give rise to differentiated progeny in a unidirectional manner. Once a CSC has exited the CSC state, it cannot re-enter it (Bonnet & Dick, 1997; Visvader & Lindeman, 2012; Chaffer et al., 2013). However, increasing evidence has revealed a remarkable amount of plasticity, where epithelial cells can dedifferentiate and re-enter the stem cell state through an EMT (Mani et al., 2008; Morel et al., 2008; Chaffer et al., 2011; Gupta et al., 2011; Chaffer et al., 2013), especially induced by EMT-TFs, such as Twist, Snail, ZEB1 or Six1 (Mani et al., 2008; McCoy et al., 2009; Chaffer et al., 2011; Gupta et al., 2011; Chaffer et al., 2013). We recently reported our human kinase cDNA screen study where we identified several novel EMT regulators and uncovered that serine/threonine kinase cyclin-dependent kinase-like 2 (CDKL2) could also confer human mammary gland epithelial cells with stem-like phenotypes through EMT (L. Li et al., 2014). After all, cancer has been proposed to be a disease of dedifferentiation (Harris, 2005).

To match different metabolic demands of variously differentiated cell types, a fundamental shift in the metabolic landscape is required (Cairns et al., 2011; Agathocleous & Harris, 2013; Shyh-Chang et al., 2013a). Compared to more differentiated epithelial cells, CSCs are characterized by a distinctive undifferentiated state, not by increased proliferation. In fact, they are often less proliferative (Agathocleous & Harris, 2013; Shyh-Chang et al., 2013a). This raises the possibility that metabolic changes observed in cancer and associated EMT are related to both the anabolic needs of proliferation and the maintenance of an undifferentiated state.

The alteration of cellular metabolism, a crucial hallmark of cancer, plays a major role during development and in stem cells (Agathocleous & Harris, 2013). The best characterized metabolic phenotype observed in tumor cells is the Warburg effect, which is a shift of ATP generation from oxidative phosphorylation to glycolysis, where glucose is converted to lactate at high rates even in oxygen-rich conditions (Warburg, 1956). Warburg hypothesized that this altered metabolism was specific to cancer cells, and it arose from mitochondrial defects that inhibited their ability to effectively oxidize glucose carbon to CO_2 (Warburg, 1956). However, increasing evidence indicates that most tumor mitochondria are not defective in their ability to carry out oxidative phosphorylation (Vander Heiden et al., 2009; Koppenol et al., 2011; Ward & Thompson, 2012). A cancer cell, like any normal cell, must obtain the building blocks that are required for the synthesis of lipids, nucleotides and amino acids. Without sufficient precursors, rapid cell proliferation will halt. In other words, ATP is not the sole metabolic requirement of tumor cells. Instead, in dividing cells, mitochondria metabolism is programmed to meet the challenges of macromolecular synthesis, and aerobic glycolysis provides a biosynthetic advantage for tumor cells — a high flux of substrate allowing for effective shunting of glucose carbons to key subsidiary biosynthetic pathways (Vander Heiden et al., 2009; Koppenol et al., 2011; Ward & Thompson, 2012; Upadhyay et al., 2013). Recently, further evidence reveals that aerobic glycolysis can also be used by some normal and cancer cells to minimize reactive oxygen species (ROS) (Anastasiou et al., 2011), a major source of metabolic damage to cells generated in part through oxidative phosphorylation. Taken together, aerobic glycolysis better satisfies the three basic needs of dividing cells: rapid ATP generation to maintain energy status, increased biosynthesis of macromolecules, and tightened maintenance of appropriate cellular redox status (Cairns et al., 2011); which is the most prevalent explanation for aerobic glycolysis in tumors and termed as the post-Warburg model (Cairns et al., 2011). In a word, aerobic glycolysis, the most common metabolic alteration in cancer cells, not only promotes ATP resources described as the Warburg model (Warburg, 1956), but also supports macromolecular biosynthesis and redox control as revised in the post-Warburg model (Cairns et al., 2011). In line with the post-Warburg model, aerobic glycolysis is associated with both cancer and normal cell proliferation, and is inhibited upon differentiation to a postmitotic cell (Agathocleous & Harris, 2013). Thus, aerobic glycolysis might be involved in regulating cell differentiation. Indeed, several studies have revealed that the differentiation of embryonic stem cells (ESCs) to cardiomyocytes and fibroblasts involves upregulation of oxidative phosphorylation and downregulation of glycolysis (Chung et al., 2007). Similarly, differentiation of human mesenchymal stem cells to adipocytes requires increased oxidative phosphorylation and ROS generation from mitochondrial complex III (Tormos et al., 2011). The reverse route, reprogramming fibroblasts to induced pluripotent stem cells