Autophagy in Metabolic Regulation of Cancer Stem Cells

Subjects: Cell Biology

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The presence of a specific population of cells within the tumor mass, commonly known as cancer stem cells (CSCs), is thought to initiate tumor formation, maintenance, resistance, and recurrence. Understanding the molecular mechanisms involved in CSC proliferation, self-renewal, and dormancy may provide important clues for developing effective therapeutic strategies. Autophagy, a catabolic process, has long been recognized to regulate various physiological and pathological processes. In addition to regulating cancer cells, studies have identified a critical role for autophagy in regulating CSC functions. Autophagy is activated under various adverse conditions and promotes cellular maintenance, survival, and even cell death.

Keywords: cancer stem cells ; autophagy ; metabolic reprogramming ; metabolic pathway ; metabolic plasticity

1. Introduction

Cancer remains the second leading cause of death worldwide [1]. Despite significant efforts from researchers and clinicians, cancer is still considered a death sentence, which is even true for high-grade malignancies. High mortality among cancer patients largely occurs because of tumors' resistance to existing therapies, which leads to recurrence. To develop effective therapies, it is important to understand the process of tumorigenesis and the specific molecular pathways that need to be targeted to overcome therapeutic resistance.

Based on extensive research, it has been identified that the majority of tumors are derived from cancer stem cells (CSCs), which are transformed from normal stem cells (SCs) or differentiated cells due to various genetic or epigenetic alterations [2]. In the late 1990s, John Edgar Dick's group pioneered the discovery of cancer stem cells (CSCs) by proposing a leukemia-initiating cell hierarchy model. This model suggested that human acute myeloid leukemia (AML) follows a hierarchical organization originating from primitive hematopoietic cells [3].

Subsequently, similar populations of CSCs were identified in various solid tumors, spanning breast, brain, prostate, ovarian, gastric, lung, and pancreatic cancers [4][5][6][7]. These CSCs were identified as a rare population of primitive cells that were long lived, could exist in proliferative or quiescent/dormant stages, were apoptosis resistant, multipotent, and most importantly possessed self-renewal capacity. This led to the proposal that CSCs are the seed of cancer and are responsible for tumor initiation, progression, and cellular heterogeneity, resistance to therapies, recurrence, and metastasis. However, the molecular mechanisms determining the proliferation/differentiation, chemoresistance, and other characteristics of CSCs are highly complex and remain poorly defined [8].

Autophagy is a catabolic process that involves the degradation of dysfunctional or unwanted cellular components through cellular lysosomal machinery. Autophagy serves to maintain cellular homeostasis under physiological conditions and is also activated under various pathological conditions and determines the outcome of the disease. The role of autophagy in CSC maintenance, proliferation, differentiation, and resistance to therapies is emerging [9][10][11][12][13]. Thus, autophagy is considered a potential therapeutic target in various cancers to eliminate CSCs.

To meet the bioenergetic, biosynthetic, and redox demands of cancer cells, various genotypic or phenotypic changes are both direct and indirect consequences of oncogenic mutations. Cancer cells display distinct metabolic phenotypes compared with their normal counterparts, which are referred to as "metabolic reprogramming" and are a "hallmark of cancer cells" [14]. Interestingly, heterogeneity among the tumor cell types was also observed at the metabolic level.

2. Metabolic Reprogramming of Cancer Cells

Because of metabolic reprogramming, changes in both intracellular and extracellular metabolites are observed in cancer cells that further regulate gene expression, cellular differentiation, and the tumor microenvironment. By undergoing metabolic changes, cancer cells develop the advantage of acquiring necessary nutrients from a nutrient-deficient environment to maintain their viability and proliferative state. Metabolic reprogramming of cancer cells mainly includes deregulated uptake of glucose and amino acids, nutrient acquisition, use of glycolysis/TCA cycle intermediates for biosynthesis and NADPH production, increased demand for nitrogen, altered gene regulation, and interaction with the microenvironment. Such changes promote tumorigenesis by facilitating and enabling processes required for rapid proliferation, survival, invasion, metastasis, and resistance to therapies [14].

3. Metabolic Alteration in CSCs

Notably, cancer stem cells (CSCs) possess a unique metabolism that differs from that of non-CSCs, enabling them to sustain their stem-like characteristics. In CSCs, these metabolic pathways are regulated by various signaling cascade, including Hippo, WNT/β-catenin, JAK/STAT, and Notch [15]. Contradictory reports complicate matters by indicating that CSCs might favor glycolysis or depend on oxidative phosphorylation (OXPHOS) for their energy needs. It is evident that CSCs display metabolic flexibility, relying on glycolytic and/or oxidative metabolism depending on the microenvironment and energy demands [16].

In normoxic tumors, heterogeneity is observed in terms of metabolic pathways adapted by CSCs; upregulation of glycolytic enzymes and dependence on mitochondrial pathways as well as mitochondrial fatty acid oxidation (FAO) for generation of ATP and NAD^+ has been observed [17]. However, under hypoxia, glycolysis is upregulated and is mediated by HIF-1α that promotes upregulation and activation of several glycolytic proteins, including glycolytic enzymes and glucose transporters [18]. Interestingly, CSCs induced by epithelial-to-mesenchymal transition demonstrate higher uptake of extracellular catabolites, such as pyruvate, lactate, glutamine, glutamate, alanine, and ketone bodies [19]. Furthermore, quiescent disseminated tumor cells rely on alternative energy sources such as autophagy [20].

4. Role of Autophagy in Regulating the Metabolic Pathway of CSCs

The role of autophagy in regulating cellular metabolism under physiological and pathological conditions is well established [20][21][22][23][24]. Autophagy is often used as an alternative pathway to meet the metabolic demands of cells under conditions of stress or nutritional and oxygen deprivation. Tumor cells activate autophagy as a cellular stress response or to meet increased metabolic demands. The role of autophagy in promoting cell survival has also been attributed to its role in energy production, which promotes tumor growth and therapeutic resistance [25]. Interestingly, earlier studies have demonstrated that autophagy and microlipophagy are as critical as electron transport chain activity and represent a strategy for SCs to maintain their energetic balance, which is crucial for their survival. Similar to SCs, CSCs are also metabolically distinct from their differentiated counterparts [26]. Various studies have provided evidence that autophagy governs metabolic pathways in CSCs [27]. CD133-expressing GSCs show better survival under nutrient deprivation conditions. It was suggested that CD133 is involved in the autophagic process under such conditions, translocates to the cytoplasm, contributes to the membrane source of the autophagosomes, is ultimately degraded by lysosomes, and promotes cell survival [28].

5. Autophagy and Metabolic Plasticity of CSCs

Emerging data suggest a role of autophagy as a key regulator of metabolic plasticity that promotes the metabolic adaptability of CSCs in the vigorous microenvironment and enables these cells to survive in hypoxic, nutrient-deficient niches [13]. Autophagy regulates CSC metabolism by controlling the cellular redox state, lipid metabolism, and dependency of CSCs on amino acids or ketone bodies and other metabolites [13][27][29]. It has been shown that high-energy metabolites such as lactate and ketones promote tumor growth and metastasis [30] and promote CSC stemness [31]. The role of autophagy has been shown to be involved in lactate production and secretion in heat stress-immature Sertoli cells [32]. Inhibition of autophagy decreased the proportion of CSCs and glycolytic gene expression in urothelial carcinoma (UC) cells, suggesting that autophagy could provide energy and nutrients for CSCs to maintain their stemness [33].

The metabolic plasticity of CSCs allows them to produce energy through various pathways that not only promote survival and support metastatic growth but also provide resistance under various adverse conditions and therapeutic agents [15]. In an important study, based on transcriptomic and metabolomics analysis data, a molecular link between autophagy and

metabolic mechanisms was suggested in CSCs, where autophagy supports the survival of these cells [34]. This study illustrated that in pancreatic ductal adenocarcinoma (PDAC), even after oncogene ablation of mutated KRAS and p53, the primary drivers of PDAC, a subset of quiescent tumor cells exhibiting characteristics of CSCs persists. These cells are accountable for tumor recurrence. Based on transcriptomic and metabolic analyses of these cells, the expressions of various genes involved in mitochondrial function, autophagy, and lysosomal activity were identified. Importantly, strong reliance on mitochondrial respiration and decreased dependence on glycolysis for cellular energetics were identified as prominent features of these surviving CSCs. Targeting mitochondrial respiration significantly inhibited the survival of these cells and hampered their tumorigenic potential. Overall, the study suggested that mitochondrial electron transport activity was strongly dependent on autophagic processes. Furthermore, in another study, it was observed that deletion of an SRC activator and neural precursor cell expressed developmentally downregulated 9 (NEDD9), a scaffolding protein that is crucial for tumorigenesis and metastases, in KRAS, and Trp 53 mutated NLCSCs showed elevated levels of LKB1 and AMPK, which fuel tumor growth by increasing autophagy [35]. Therefore, targeting the KRAS pathway along with mitochondrial respiration appears to be a potential target for the elimination of bulk tumor cells along with the dormant CSC population [34].

6. Autophagy Regulates Metabolic Adaptations in the Tumor Microenvironment and Cancer Stem Cells

In addition to the direct regulation of CSC metabolic functions, metabolic reprograming is also observed in cancer-associated fibroblasts, which are key components of the CSC microenvironment that rely more on aerobic glycolysis than oxidative phosphorylation [36]. Simultaneously, these cells also show upregulation of autophagic programs to support their proliferative and migratory capability, along with secretion of cytokines and growth factors [37][38]. Moreover, autophagy-derived catabolic substrates from cancer-associated fibroblasts also support the energy needs of pancreatic ductal adenocarcinoma [24][39]. An important role of autophagy has been observed during nutrient-poor states during which quiescent disseminated tumor cells rely mainly on autophagy to meet the energy demand and promote cell survival in harsh environments.

Overall, autophagy upregulation in CSCs promotes metabolic homeostasis and survival under various harmful conditions faced by these cells, such as starvation, energy deficiency, hypoxia, or anticancer treatment.

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