Hematopoiesis

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1. Introduction

Hematopoiesis is a stepwise process through which hematopoietic stem cells (HSCs) differentiate to progenitor cells that demonstrate a restricted potential and eventually further differentiate to form all mature blood and immune cells. Effective hematopoiesis depends on the strict regulation of quiescence, self-renewal, and differentiation of HSCs. Healthy HSCs rely heavily on bone marrow oxygen tension to retain their stemness, and they do so by altering their gene expression to fit a more glycolytic rather than mitochondrial metabolic profile [1][2]. Differentiation commitment is reflected by a metabolic switch from Warburg glycolysis to the mitochondrial tricarboxylic acid cycle (TCA) and oxidative phosphorylation (OXPHOS) [1][2]. Malignant cells tend to rewire their metabolism to meet up with their high energy requirements for growth and proliferation. Metabolic reprogramming serves two main goals: first, rapid adenosine triphosphate (ATP) production and adequate supply of intermediates for the synthesis of nucleotides, amino acids, lipids, and redox molecules; second, the rewiring of nutrient sensing pathways [3]. Metabolic pathway aberrations, including glycolysis, the TCA cycle, and fatty acid metabolism, have been implicated in hematologic malignancies, especially leukemia [4].

2. Autophagy and Metabolism in Normal and Malignant Hematopoiesis

Autophagy is the major intracellular degradation system by which cytoplasmic components are delivered to and degraded in the lysosome. Double-membrane vesicles, termed autophagosomes, engulf long-lived proteins or damaged organelles and transport these cargos to the lysosomes. There, the outer membrane of the autophagosome fuses with the lysosomal membrane, and the inner vesicle, together with its cargo, is degraded. The resulting macromolecules can be recycled back to the cytosol. The autophagic process serves a dual role: first, removal of damaged intracellular organelles; second, recycling of cellular contents, to support metabolites and basic building blocks required in anabolic processes, such as cell growth, proliferation, remodeling, and differentiation [5]. Autophagy has been shown to be essential for HSCs maintenance [6], while transcription factors, considered to be master regulators of hematopoiesis, exert their transcriptional control on autophagy-related genes [7][8]. Autophagy works to satisfy distinct metabolic demands during HSCs differentiation. The cellular mitochondrial content, as well as mitochondrial quality, defines the adequacy of OXPHOS, and thus ATP production, but, at the same time, the reactive oxygen species (ROS) levels. Mitophagy regulation during normal hematopoiesis serves the different metabolic requirements of hematopoietic cells from the HSC stage to mature blood cells and also controls the degree of DNA damage, through ROS modulation. Distinct levels of mitochondrial content and activity are a prerequisite for the maintenance and differentiation of hematopoietic stem/progenitor cells (HSPCs); hence, an optimal amount of mitophagy is critical. Hyperactivated mitophagy results in diminished mitochondrial activity, resulting in various hematopoietic disorders, such as aplastic anemia, hematological malignancies, and aging-associated diseases. Though research in leukemogenesis concentrates on recurrent genetic and epigenetic aberrations [9], recent data unravel that epigenome modulations contribute to the metabolic reprogramming of leukemic cells, while metabolites may conversely regulate epigenetic events [10]. This review focuses on the role of autophagy and metabolism during normal hematopoiesis, as well as on their perturbations during malignant hematopoiesis, with a focus on leukemogenesis.

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