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Review

Mitochondrial dependency in progression of acute myeloid leukemia

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ABSTRACT

Acute myeloid leukemia (AML) is a clonal hematopoietic malignant disorder which arises due to dysregulated differentiation, uncontrolled growth and inhibition of apoptosis leading to the accumulation of immature myeloid progenitor in the bone marrow. The heterogeneity of the disease at the molecular and cytogenetic level has led to the identification of several alteration of biological and clinical significance. One of the alterations which have gained attention in recent times is the altered energy and metabolic dependency of cancer originally proposed by Warburg. Mitochondria are important cell organelles regulating cellular energetic level, metabolism and apoptosis which in turn can affect cell proliferation and differentiation, the major manifestations of diseases like AML. In recent times the importance of mitochondrial generated ATP and mitochondrial localized metabolic pathways has been shown to play important role in the progression of AML. These studies have also demonstrated the clinical significance of mitochondrial targets for its effectiveness in combating relapsed or refractory AML. Here we review the importance of the mitochondrial dependency for the progression of AML and the emergence of the mitochondrial molecular targets which holds therapeutic importance.

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1. Acute myeloid leukemia

Acute myeloid leukemia (AML) is characterized by malignant clonal proliferation of immature myeloid progenitor cells in the bone marrow and peripheral blood. Commonly, AML is considered to be the result of genetic aberrations leading to irreversible deregulation of functions of genes critical for proliferation, differentiation, apoptosis and gene transcription. Based on the WHO 2008 classification, acute myeloid leukemia are classified as: acute myeloid leukemia with recurrent genetic abnormalities, acute myeloid leukemia with myelodysplasia-related changes, therapy-related myeloid neoplasms, acute myeloid leukemia, not otherwise specified, myeloid sarcoma, myeloid proliferations related to Down syndrome and blastic plasmacytoid dendritic cell neoplasm (Vardiman et al., 2009). Some of the types which fall under genetic abnormalities are AML with t(8;21)(q22;q22); RUNX1–RUNX1T1; AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11; acute promyelocytic leukemia (APL) with t(15;17)(q22;q12); PML–RARA *etc*. These genetic rearrangements give the cells growth advantage by activating downstream effectors of various signaling pathways which make the cells insensitive towards growth signals and alter the expression of key transcriptional targets in myeloid differentiation (Renneville et al., 2008). The other important feature of the disease is the existence of leukemic stem cells (LSCs) which has been considered as a major cause of relapse in acute myeloid leukemia as these are insensitive to conventional chemotherapeutic techniques (Krause and Van Etten, 2007). These leukemic stem cells are also being considered to

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be the initiator of the malignancy (Shlush et al., 2014). Hence the identification and eradication of these dormant LSCs are of therapeutic importance.

The present chemotherapeutic approach is based on the concept of targeting leukemic cells specifically to eradicate them while minimally affecting normal cells. Genetic alterations have led to the identification of mutations in cell proliferation related genes like Fms-like tyrosine kinase 3 (FLT3), c-KIT, RAS *etc*., and genes involved in prevention of apoptosis like Nucleophosmin (NPM1), p53 *etc*. These genetic alterations have been used for cytogenetic analysis at time of diagnosis and are used as a prognostic factor of clinical outcome in AML and characterize the disease into favorable and unfavorable prognosis (Patel et al., 2012). These genetic alterations are potential therapeutic targets but many of these approaches fail to show sufficient activity against the broad range of cell types which occur in AML. The inherent genetic, epigenetic and cellular heterogeneity is a significant factor underlying the limitations of targeted agents. On the other hand recent studies are focusing on targeting basic physiological properties like cellular metabolism, nutrient sensing and mitochondrial functionality which are expected to be similar irrespective of the genetic makeup of the cell. These studies not only show the importance of metabolism and mitochondrial functionality in maintaining leukemic cells but are also emerging as potential drug targets.

2. Altered metabolism in cancer and the mitochondria

Increasing evidences suggests that deranged metabolism is an important mechanism of cancer pathogenesis. More than fifty years ago Warburg hypothesized that altered metabolism was specific to cancer cells, and that it arose from mitochondrial defects that inhibited their ability to effectively oxidize glucose carbon to CO_2 (Warburg, 1956). Warburg's hypothesis has been observed in a wide variety of cancers and has been exploited clinically by using 18-F-deoxyglucose positron emission tomography (FDG-PET) for detection of malignant tissues (Gambhir, 2002). The process of glycolysis leads to the production of pyruvate from glucose. Under aerobic condition pyruvate is transported into the mitochondria for further oxidation and under anaerobic condition pyruvate is converted to lactate in the cytosol. Based on Warburg hypothesis cancer cells undergo metabolic reprogramming to perform aerobic glycolysis. An extension of this hypothesis was that dysfunctional mitochondria caused cancer. But contrary to this conventional idea functional mitochondria are essential for the cancer cell. Mitochondria perform a wide array of functions for the cell contributing to its survival. The most important function of the mitochondria for which it is often referred to as the 'power house' of the cell is the production of ATP by oxidative phosphorylation (OXPHOS). The OXPHOS system consists of five multisubunit complexes embedded in the mitochondria inner membrane — NADH:ubiquinone oxidoreductase (complex I), succinate:ubiquinone oxidoreductase (complex II), ubiquinol:cytochrome c oxidoreductase (complex III), cytochrome c oxidase (complex IV) and F_0 F_1-ATP-synthase (complex V). The OXPHOS has two functional parts, the four complexes complex I to IV comprise the electron transport chain (ETC.) and complex V synthesizes ATP. The human mitochondria consist of a 16.6 kb circular mitochondrial DNA (mtDNA) located within the mitochondria (Falkenberg et al., 2007). The mitochondrial genome encodes two rRNAs, 22 t-RNAs and 13 of the 90 proteins in the mitochondrial respiratory chain. Mitochondria can maintain their own genome, and have a full-fledged replication, transcription and translational machinery. Their circular genome codes for 13 mRNAs so most of the proteins are coded by the nuclear genome and the proteins are transported into the mitochondria with specialized transporting machinery (Neupert and Herrmann, 2007). Mitochondria also consist of core metabolic pathways like Krebs cycle, fatty acid oxidation and amino acid metabolism which play major role in metabolizing carbohydrates, lipids and amino acids. They participate in energy production by mitochondria and other metabolic pathways by producing high energy intermediates NADH, NADPH and $FADH_2$ (Chiarugi et al., 2012). Again mitochondria are the main site of ROS production in cells and this is a byproduct of the aerobic metabolism (Turrens, 2003). The mitochondrial ROS generation has been reported to cause cancerous transformations (DeBerardinis and Cheng, 2010). Another hallmark of cancer is the evasion of cell death by bypassing the apoptotic signals. Mitochondria are an important site of apoptosis pathway (Green and Kroemer, 2004). Interestingly, recent studies indicate that the cell proliferation, apoptosis and metabolism are interconnected and the mitochondria are the hub where both the metabolic and the apoptotic signaling integrate (Andersen and Kornbluth, 2013). In cancerous tissues thus the mitochondria are not dysfunctional but rather have altered functionality in comparison to normal cells (Wallace, 2012).

In cancer studies involving mtDNA mutation and its effect on OXPHOS demonstrated that the mutations do not inactivate mitochondrial energy metabolism but alters the bioenergetic and metabolic state of the cell. Apart from mtDNA, mutations of the nDNA encoded mitochondrial enzymes also influences the metabolic pathways. The enzymes found to be mutated in various types of cancer are succinate dehydrogenase subunits (Selak et al., 2005), fumarate hydratase (Isaacs et al., 2005), isocitrate dehydrogenase isoforms (Yan et al., 2009) and carnitine palmitoyltransferase (Zaugg et al., 2011). The oncogenes and tumor suppressor genes which play a role in regulating cell cycle, sustenance of proliferative signals, evasion of growth suppression and cell death are now being considered to reprogram the cellular metabolism (Levine and Puzio-Kuter, 2010). This reprogramming of cellular metabolism also involves regulating the mitochondrial metabolic pathways, OXPHOS and mitochondrial biogenesis (Munoz-Pinedo et al., 2012).

For combating a genetically heterogenous disease like AML, targeting the cellular metabolism and mitochondrial functionality is being explored. The interplay between dependencies on mitochondrial metabolism and glycolytic flux in leukemia cells remains to be determined, but both represent potential therapeutic or prognostic targets for the treatment of AML (Jaras and Ebert, 2011). Recent work on metabolomic based characterization of cytogenetically normal AML patient serum samples highlighted an increase in glycolytic markers. It was also shown that more glycolytic cells were less sensitive to chemotherapeutic drug arabinofuranosyl cytidine (Ara-C) (Chen et al., 2014). Previously it was demonstrated that highly glycolytic AML blast cells were more resistant to chemotherapeutic drugs all-trans retinoic acid (ATRA) and/or arsenic trioxide (ATO) (Herst et al., 2011). Interestingly recent studies have shown the importance of mitochondrial OXPHOS and other mitochondrially localized metabolic pathways for the progression and maintenance of AML. In this review we take a closer look at these studies which explore the status of the mitochondrially localized metabolic pathways which contribute to energy and metabolic homeostasis of the whole cell. We also discuss the effect of cellular metabolism on apoptosis, autophagy and redox signaling, which are intricately related to mitochondrial functionality, and their role in AML progression and response during chemotherapy. Finally, this study will highlight the dependency on the mitochondria for the progression of AML and the prospect of therapeutically targeting the various mitochondrial pathways.

3. Mitochondrial oxidative phosphorylation system and AML

Somatic and germline mutations of mtDNA have been studied across various types of cancer. These studies attempt to correlate mtDNA mutations with the OXPHOS function and its role in neoplastic transformation (Chatterjee et al., 2006). Earlier studies have shown that the mtDNA amounts are amplified in comparison to nDNA in the blast cells of AML (Boultwood et al., 1996). Studies of mtDNA mutation in both pediatric AML (Sharawat et al., 2009) and in adult AML (Silkjaer et al., 2013) showed mutations in the regulatory D-loop region and non-synonymous mutation in COI (complex IV subunit). COI mutations are known to be associated with neoplastic transformation (Petros et al.,