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Title  
Metabolic flexibility and mitochondrial OxPHOS activity in the drug resistance of leukemia

Abstract  
Metabolic reprogramming is now considered one of the major characteristics of cancer cells as they must adapt their metabolism to fuel energetic and biosynthetic needs for proliferation (Boroughs and DeBerardinis, 2015; Léhuédé et al. 2016; Martinez-Outschoorn et al. 2016; Vander Heiden and DeBerardinis, 2017). Changes in intermediary and energy metabolism are also a key hallmark of acute myeloid leukemia (AML), and targeting glycolysis, glutaminolysis, fatty acid β-oxidation or mitochondrial oxidative phosphorylation (OxPHOS) are promising anti-leukemic approaches (Samudio et al. 2010; Skrtic et al. 2011; Scotland et al 2013; Jacque et al. 2015; Matre et al. 2016; Poulain et al. 2017).

Several groups have shown that drug-resistant cancer cells rely on High OxPHOS and mitochondrial function in some types of cancers including myeloid malignancies (Kuntz et al. 2017; Farge et al. 2017; Lee et al. 2017; Bosc et al. 2017). However, the role of the cell metabolism into the mitochondrial-driven drug resistance remains largely unknown. Furthermore, recurrent mutations in genes of two crucial metabolic enzymes, isocitrate dehydrogenase 1 and 2, have been discovered in more than 15% of AML patients (Mardis et al. 2009; Abbas et al. 2010; Marcucci et al. 2010; Paschka et al. 2010) and represent new therapeutic targets (Rohle et al. 2013; Wang et al. 2013; Yen et al. 2017). Whereas wild-type IDH1 catalyzes the conversion of isocitrate to α-ketoglutarate (α-KG) generating NADPH in the cytosol, mutant IDH1 catalyzes a neomorphic enzyme activity that produces the oncometabolite R-2-hydroxyglutarate (2-HG) from α-KG (Dang et al. 2009; Ward et al. 2010), thereby limiting the availability and utilization of this latter key metabolite central to intermediary metabolism, and oxidizes NADPH. The impact of IDH mutation and its oncometabolite have been well documented on alteration of DNA and histone methylation and imbalance in myeloid/erythroid differentiation through 2-HG-dependent allosteric competitive inhibition of multiple α-KG-dependent dioxygenases and other enzymes (Figueroa et al. 2010; Sasaki et al. 2012; Losman et al. 2013; Kats et al. 2014; Boutzen et al. 2016). However, the contribution of IDH mutation to cell intermediary metabolism and α-KG homeostasis is not fully understood in AML and its chemoresistance. Here we will discuss about the role of the metabolic reprogramming in the drug resistance in cancer, especially in mutant IDH1-driven tumor models, providing a strong scientific rationale for clinical trials of innovative combinatory targeted therapies to selectively treat this subset of patients, especially those insensitive to newly-FDA approved IDH mutant-specific inhibitors. In conclusion, we will speculate about the notion that leukemia and cancers are metabolic and bioenergetic (oncogenetic-driven?) syndromes that could form the basis of precision metabolic medicine.