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Abstract Title : Rewiring lipid metabolism: A novel approach to overcome drug resistance in multiple myeloma

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Review Category: Multiple Myeloma and Plasma Cell Dyscrasias: Basic and Translational

Authors

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Abstract Body

Despite significant therapeutic advancements in multiple myeloma (MM) treatment, which have improved patient outcomes and extended survival, most patients experience relapse or are non-responsive to therapy, leading to relapsed/refractory multiple myeloma (RRMM). The disease's complex progression, driven by intricate molecular mechanisms and genetic alterations, contributes to its resistance phenotype, underscoring an urgent need for innovative strategies to improve patient outcomes.

Myeloma cells undergo extensive metabolic reprogramming to sustain rapid proliferation and survival. A key feature of this reprogramming is altered lipid metabolism, particularly the dysregulation of de novo fatty acid synthesis. Recent studies have identified *de novo* lipogenesis (DNL) as a critical metabolic vulnerability in MM. In our study, we characterized a novel *de novo* lipogenesis inhibitor (DNL-I) designed to target lipid metabolism in MM. DNL-I disrupts lipid homeostasis by selectively inhibiting de novo lipogenesis, the biosynthetic pathway responsible for endogenous fatty acid production.

Our findings demonstrate that DNL-I potently induces apoptosis in both MM cells sensitive to standard therapies and those resistant to proteasome inhibitors (PI). The apoptotic effect was dose-dependent, with increasing concentrations of DNL-I correlating with enhanced cell death across multiple MM cell lines. Mechanistically, we found that DNL-I downregulates the expression of key enzymes involved in fatty acid synthesis, such as acetyl-CoA carboxylase (ACC) and fatty acid synthase (FASN), without altering the expression or activity of enzymes associated with fatty acid β-oxidation, such as carnitine palmitoyltransferase 1 (CPT1). This selective inhibition confirms that DNL-I specifically targets de novo lipogenesis, a pathway increasingly recognized as a vulnerability in cancer cells reliant on lipid availability for membrane biogenesis and signalling. Particularly, we conducted rescue experiments to validate the role of lipid depletion in DNL-I's mechanism of action. Supplementing MM cells with an exogenous lipid mixture containing arachidonic, linoleic, linolenic, myristic, oleic, palmitic, and stearic acids fully reversed DNL-I-induced apoptosis in both sensitive and PI-resistant MM cell lines. This reversal suggests that the cytotoxic effects of DNL-I stem directly from its disruption of lipid availability, which is essential for MM cell survival and proliferation.

Notably, untargeted metabolomic analyses of DNL-I-treated MM cells revealed significant alterations in amino acid metabolism, the tricarboxylic acid (TCA) cycle, and sphingolipid metabolism, all of which are essential for MM cell survival. These findings highlight the therapeutic potential of targeting *de novo* lipogenesis in MM, particularly for overcoming resistance to proteasome inhibitors, and underscore the importance of lipid metabolism as a novel therapeutic target in this disease.

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