“Investigating the role of Dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A) in the response of cancer cells to chemotherapy”

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Abstract:
Up till now, resistance to chemotherapy has been the major hurdle in controlling cancer. Chemoresistance is thought to be, at least in part, the result of the inherent heterogeneity found in genetically unstable tumors. Cancer resistance could result in new vulnerabilities that can be targeted. This acquired vulnerability of drug-resistant cells is also referred to as ‘collateral sensitivity’. The process usually starts very early during therapy, but shows up after a few cycles of treatment. Developing new strategies to enhance ‘collateral sensitivity’ may be achieved through manipulating cell quiescence. Cellular quiescence is also identified as a major contributor to tumor recurrence and aggressiveness. It is a reversible state of cell cycle arrest induced after exposure to chemotherapy and stressful conditions. So far, there are only a few studies that explored the molecular players involved in cancer cell quiescence. The Dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A), (also known as Down syndrome related kinase) was found to be associated with neurogenesis defects through affecting the cell cycle progression and the induction of premature differentiation to neuronal cells. DYRK1A causes cell cycle arrest at G0-G1 through phosphorylation of cyclin D leading to its degradation; and phosphorylation of P27 Kip resulting in its stabilization. Moreover, DYRK1A enhances DREAM complex assembly, which inhibits transcription of cell cycle genes in G0/G1 phase and subsequently induces cell quiescence. Based on our preliminary results, DYRK1A inhibitors sensitize various cancer cells to chemotherapeutic drugs. Intriguingly, the transcriptomic data showed that cancer cell-quiescence related pathways (e.g. autophagy) are downregulated in DYRK1A depleted cells. The role of DYRK1A in cancer cell quiescence pathways and the response of cancer cells to chemotherapy have not been clearly investigated. In this project our aim is to investigate the critical role of DYRK1A in cancer cell quiescence and its effect on cellular response to chemotherapeutic drugs. The results of this study may suggest the DYRK1A inhibitors as a potential ‘collateral sensitizers’ that enhance the response of quiescent cancer cells to the conventional chemotherapeutic drugs.

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