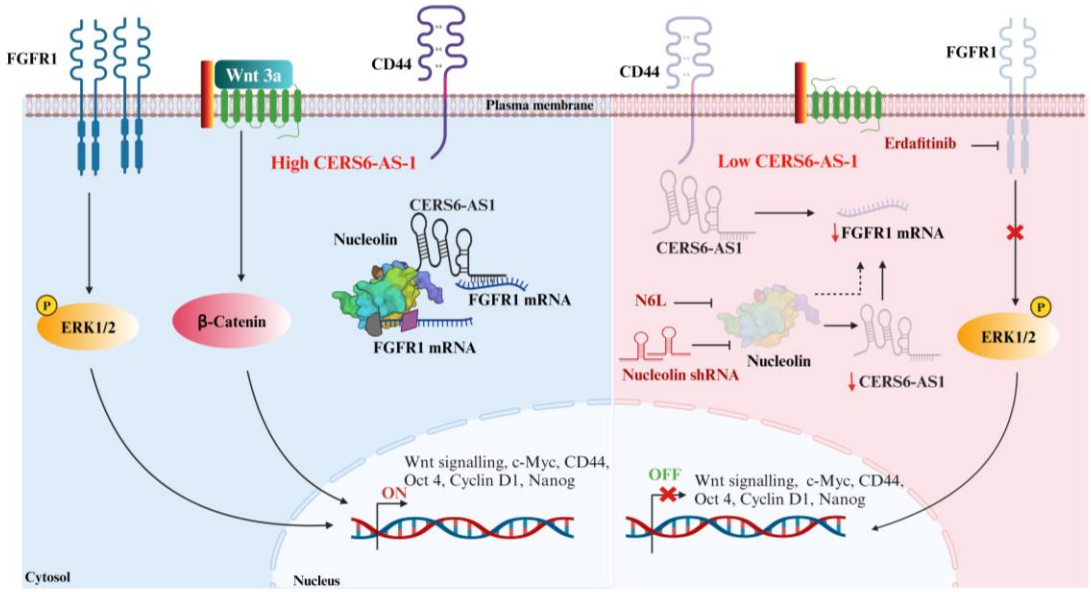
Targeting CERS6-AS1/FGFR1 axis as synthetic vulnerability to constrain stromal cells supported proliferation in Mantle cell lymphoma

Mantle cell lymphoma (MCL) is considered an incurable subtype of B-cell lymphoma with significant bone marrow involvement (60-80%). Despite of multiple treatment options, high rates of MCL relapse cases suggests its incomplete elimination. The interaction between stromal and tumor cells in tumor microenvironment is a crucial factor in MCL progression and therapy resistance. We have identified a long non-coding RNA, CERS6-AS1, upregulated in MCL and associated with poor overall survival. CERS6-AS1 expression was elevated in primary MCL within stromal microenvironment and in a subset of MCL cells adhered to stromal layer. These stromal-adhered MCL subsets exhibited cancer stem cell signatures than suspension counterparts. Within the stromal cell microenvironment, a subset of MCL adhered to the stromal cells layer; those directly receive growth and survival signals via adhesion molecules, and cytokines that facilitate global differences in key signaling pathways. With this notion, our patient-derived MCL adhered to stromal cells showed a significant upregulation of CERS6-AS1 expression with consistent changes in the level of cancer stem cell genes (CD44 and Nanog) and resistance to BTK inhibitors than MCL cells grown in suspension. In the present study, we found a significant increase in FGFR1 expression in MCL when grown with stromal cells, in adherent-MCL than in suspension-MCL and in $CD45^{+}CD19^{low}$ cells than $CD45^{+}CD19^{high}$ MCL cells. The observed high level of FGFR1 in multiple sets of experiments and its consistent positive correlation with CERS6-AS1 expression, Mechanistically, we found that downregulating CERS6-AS1 in MCL reduced Fibroblast Growth Factor Receptor-1 (FGFR1), expression attributed to loss of its interaction with RNA-binding protein nucleolin. LncRNAs primarily function through various mechanisms, and one significant mode of action is interacting with RBPs. Nucleolin is upregulated in various solid and liquid cancer and is uniquely localized on surface of cancer cells, a phenomenon not observed in normal cells and that's makes it an appealing target for therapeutic intervention. In addition, using in-silico approach, we have discovered a direct interaction between nucleolin and 5'UTR of FGFR1, thereby regulating FGFR1 transcript stability. We discovered a positive association of CERS6-AS1 with cancer stem cell signatures, and Wnt signaling. Building on these, we explored potential therapeutic strategies where combining nucleolin-targeting agent with FGFR1 inhibition significantly contributed to reversing cancer stem cell signatures and abrogated primary MCL cell growth on stromal layer. These findings provide mechanistic insights into regulatory network involving CERS6-AS1, nucleolin, and FGFR1 axis-associated crosstalk between tumor cells and stromal cell interaction and highlights therapeutic potential of targeting a non-coding RNA in MCL.



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