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The Current Understanding of the Mechanism of Mutant Calr-Induced Oncogenesis

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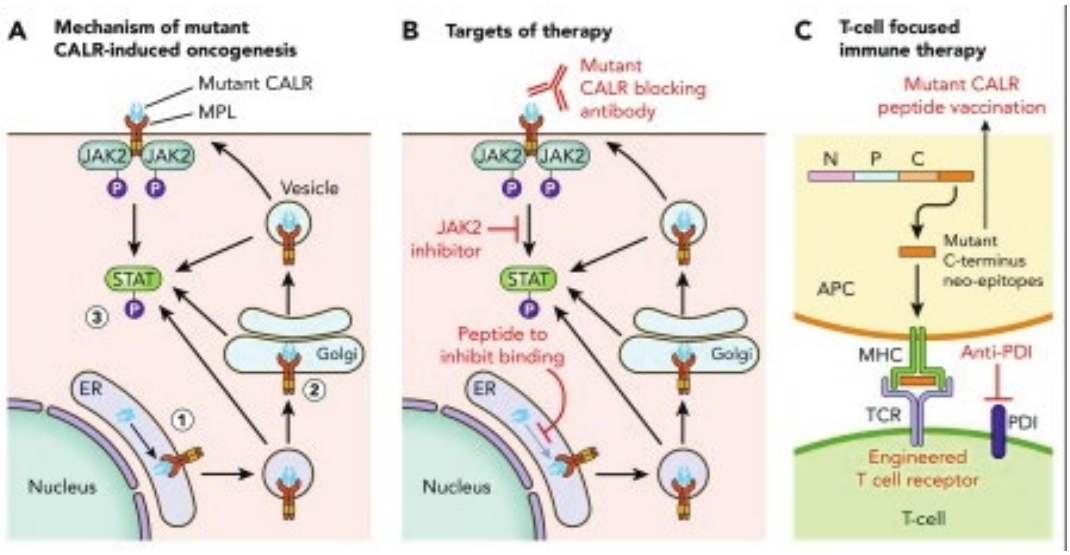

Figure 1 Mechanism of mutant CALR-induced MPN and approaches for therapeutic targeting (A): Pathogenic binding interaction between MPL and mutant CALR leads to activated MPL-JAK/STAT signaling. 1. Mutant CALR traffics through the ER to bind to immature MPL, 2. Stabilized mutant calreticulin-MPL complex traffics to the cell surface, 3. Mutant CALR induces MPL-JAK/STAT signaling pathway activation; (B): Potential nodes for therapeutic intervention in mutant-CALR-driven MPN; (C): Strategies to induce T-cell-directed immune therapy against mutant-CALR-driven MPN. APC: Antigen-Presenting Cell; MPL: Myeloproliferative Leukemia; TCR: T-Cell Receptor. For MPL activation there is a requirement of Mutant CALR entry into the ER secretory pathway and loss of mutant CALR's signal peptide revoke STAT5 transcriptional activity. After getting outside the Endoplasmic Reticulum, mutant CALR forms stable complexes with pre-processed forms of MPL containing immature N-glycosylation sites, which is dependent on mutant CALR's lectin-binding domain and then the mutant CALR-MPL complexes are present inside the Golgi apparatus further trafficked to the surface of the cell. The interaction with mutant CALR allows thrombopoietin-independent dimerization of MPL's cytosolic tails, with cell surface localization which leads to full receptor activation. Clonal expansion of long-term hematopoietic stem cells and megakaryocytes results through ligand-independent MPL-JAK/STAT signalling activation. Mutant CALR has been studied to have altered cellular localization due to loss of its C-terminal KDEL sequence, which results in new protein-binding interactions, in the nucleus.

