MUTANT CALRETICULIN DISPLAYS ABERRANT CHAPERONE ACTIVITY

Somatic frameshift mutations in calreticulin (CALR), which encodes a calcium-binding chaperone protein that regulates protein folding quality control in the endoplasmic reticulum (ER), occur in approximately 20% to 30% of patients with essential thrombocythemia and primary myelofibrosis, two types of myeloproliferative neoplasms (MPN). These mutations eliminate the ER retention signal and create a mutant-specific positively charged C-terminal tail that interacts with the thrombopoietin receptor (TPOR). Although it is known that this new C-terminus and TPOR activation are both required for oncogenic transformation by mutant CALR, the exact function of the mutant CALR protein remains unclear. Pecquet, Chachoua, Roy, Balligand, and colleagues observed that mutant CALR and TPOR colocalize outside of the ER in the Golgi network compartments and at the plasma membrane, and that the ER-to-Golgi secretory pathway is required for activation of TPOR by mutant CALR. Mutant CALR bound directly to TPOR and enhanced its stability and promoted its dimerization and localization to the plasma membrane, where it was activated in a TPO-independent manner and induced downstream JAK–STAT signaling. Mutant CALR also could promote cell-surface trafficking of immature, folding-deficient, or trafficking-impaired mutant or ER-retained TPOR protein, suggesting that MPN-associated CALR mutations endow the mutant CALR protein with rogue chaperone activity that facilitates cytokine-independent activation of TPOR at the cell surface. Furthermore, TPOR cell-surface localization was a requirement for oncogenic transformation by CALR mutants. These findings establish the fundamental consequences of the CALR mutations identified in MPN and suggest that strategies to target mutant CALR may prevent cytokine-independent TPOR activation and proliferation in MPN. ■


TRANSPOSABLE ELEMENTS REGULATE ONCOGENE EXPRESSION IN HUMAN CANCERS

Activation of epigenetically silenced transposable elements (TE) is a recently identified mechanism of oncogene activation known as onco-exaptation. Although it has been shown in specific cancer types, onco-exaptation has yet to be comprehensively analyzed as a widespread mechanism for oncogene activation. In an analysis of RNA-sequencing data from 7,769 tumor samples and 625 tumor-matched normal samples, Jang, Shah, and colleagues identified oncogene–TE chimeric transcripts in nearly 50% of all tumors. The most prevalent onco-exaptation events accounted for more than 50% of target gene expression, and up to 90% of oncogene expression in some tumors. Among highly expressed TE-regulated oncogenes was the fusion transcript AluJb–LIN28B, coding for an additional 22 amino acids on the N terminus of LIN28B. Paired-end CAGE sequencing in two lung cancer cell lines confirmed a cryptic transcription start site within the AluJb promoter 20 kb upstream of the LIN28B promoter. The AluJb promoter was completely methylated in somatic cells and either wholly or partially demethylated in cancer cells; demethylation was accompanied by an open chromatin state and active epigenetic marks. Targeted methylation or demethylation of the AluJb promoter decreased or increased expression of the AluJb–LIN28B fusion, respectively. Motif analysis identified binding motifs for C/EBPδ, SP1, SP4, and YY1 transcription factors within the AluJb promoter, and luciferase reporter assays demonstrated a loss of activity following deletion or mutation of these motifs. Deletion of the AluJb promoter, but not the LIN28B promoter, eliminated expression of the fusion protein, resulting in increased levels of LIN28B target miRNAs, slower growth and migration in vitro, and defective tumor growth in vivo; reexpression of LIN28B partially reversed these effects. Taken together, these findings show that dynamic DNA methylation within the cell can activate regulatory elements within oncogene-associated TEs to drive tumor progression. Onco-exaptation is thus a widespread mechanism of oncogene activation and represents a potential target for therapeutic intervention. ■


Myeloproliferative Neoplasms

Major finding: Mutant calreticulin promotes transport of defective TPOR proteins to the plasma membrane.

Concept: The rogue chaperone activity of mutant calreticulin is required for oncogenic transformation.

Impact: Targeting mutant calreticulin may prevent pathologic TPOR activation at the cell surface.

Oncogenes

Major finding: Activation of transposable elements (TE) upstream of oncogenes is a widespread event in cancer.

Concept: Demethylation and activation of promoters within TEs drives expression of downstream oncogenes.

Impact: Onco-exaptation is prevalent, functionally relevant, and a potential therapeutic target in cancer.
Transposable Elements Regulate Oncogene Expression in Human Cancers

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