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Noncanonical Function of AGO2 Augments T-cell Receptor Signaling in T-cell Prolymphocytic Leukemia

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T-cell prolymphocytic leukemia (T-PLL) is a chemotherapy-refractory T-cell malignancy with limited therapeutic options and a poor prognosis. Current disease concepts implicate TCL1A oncogene-mediated enhanced T-cell receptor (TCR) signaling and aberrant DNA repair as central perturbed pathways. We discovered that recurrent gains on chromosome 8q more frequently involve the argonaute RISC catalytic component 2 (AGO2) gene than the adjacent MYC locus as the affected minimally amplified genomic region. AGO2 has been understood

as a protumorigenic key regulator of miRNA (miR) processing. Here, in primary tumor material and cell line models, AGO2 overrepresentation associated (i) with higher disease burden, (ii) with enhanced in vitro viability and growth of leukemic T cells, and (iii) with miR-omes and transcriptomes that highlight altered survival signaling, abrogated cell-cycle control, and defective DNA damage responses. However, AGO2 elicited also immediate, rather non-RNA-mediated, effects in leukemic T cells. Systems of genetically modulated AGO2 revealed that it enhances TCR signaling, particularly at the level of ZAP70, PLCγ1, and LAT kinase phosphoactivation. In global mass spectrometric analyses, AGO2 interacted with a unique set of partners in a TCR-stimulated context, including the TCR kinases LCK and ZAP70, forming membranous protein complexes. Models of their three-dimensional structure also suggested that AGO2 undergoes posttranscriptional modifications by ZAP70. This novel TCR-associated noncanonical function of AGO2 represents, in addition to TCL1A-mediated TCR signal augmentation, another enhancer mechanism of this important deregulated growth pathway in T-PLL. These findings further emphasize TCR signaling intermediates as candidates for therapeutic targeting.