POSTER 27: Alteration of the tumor suppressor PDCD4 by a novel alternative splicing in acute myeloid leukemia

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Programmed cell death 4 (PDCD4) is a tumor suppressor acting mainly via inhibition of global protein synthesis next to the sequestering of general mRNA translation initiation factors. Through its RNA-binding activity, PDCD4 acts also more specifically by targeting and inhibiting the translation of mRNAs encoding proteins belonging to the BCL and IAP families of anti-apoptotic factors (including BCL2, BCLXL, BAG 1, CIAP & XIAP). As a consequence, PDCD4 participates in inhibition of cell proliferation and induction of apoptosis. In many tumors, PDCD4 is down-regulated via the PI3K-mTOR-S6K oncogenic pathway which targets the protein to degradation by the proteasome. Here, we have identified a novel mechanism of PDCD4 down-regulation occurring specifically in a sizable fraction of acute myeloid leukemia (AML) patients, and correlating strongly with a poorer overall survival. Indeed, in ~20% of patients, blasts express an alternatively spliced PDCD4 mRNA devoid of its exon 2. These blasts are enriched in hematopoietic stem cell markers, and functional experiments reveal a switch from the alternative to the normal form as blasts progress toward myeloid differentiation. As the initiator AUG is normally located in PDCD4 mRNA exon 2, translation of the alternative PDCD4 mRNA starts at the next in frame AUG located in exon 6. The resulting alternative PDCD4 protein lacks its N-terminal third which normally contains functional domains important for its tumor suppressor function. The shorter protein is likely not fully exerting its anti-oncogenic actions and, given its specific role as a repressor of anti-apoptotic factors, could represent a marker ofresponse to BCL2 inhibitors such as Venetoclax.