**POSTER 23: Identification of a new form of the PDCD4 tumor suppressor resulting from an alternative splicing in acute myeloid leukemia**

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PDCD4 (Programmed Cell Death 4) is a tumor suppressor downregulated in many cancers including AML (Acute Myeloid Leukemia). It acts as a translational inhibitor in normal cells, but its downregulation in cancer cells improves proliferation. Different functional domains support its function. The N-terminal third is an RNA-binding domain impairing ribosome scanning in general and inhibiting IRES-dependent (Internal Ribosome Entry Site) translation for several mRNAs. For example, some IRES containing mRNA encoding for anti-apoptotic factors, from BCL and IAP families, are targeted by PDCD4. The middle and C-terminal parts of PDCD4 are each composed of one MA-3 domain binding and sequestering the translation initiation factors eIF4A or eIF4G thus inhibiting the mRNA cap-dependent translation initiation.

We identified a new spliced PDCD4 mRNA form in AML patients in which exon 2 is skipped. This alternative form represents the main PDCD4 mRNA for 15% of them. As the start codon of PDCD4 protein is located in the skipped exon 2, the alternative protein starts at the next in frame initiator codon located in exon 6. This leads to the expression of a truncated PDCD4 protein devoid of its N-terminal and middle parts. We found that the level of this short PDCD4 form correlates with expression of hematopoietic stem cell markers and diminishes in favour of the full-length form during myeloid differentiation.

To better understand the roles and abilities of this shorter protein, we developed inducible lentivector-transduced AML cell lines reproducing the expression of the short protein (HA-tagged), with either a PDCD4 sequence where the first start codon in exon 2 has been mutated or a PDCD4 sequence where the whole exon 2 has been removed.

Devoid of its RNA-binding domain and of one of its MA-3 domains, the short form seems to still bind eIF4A. However, due to its very weak expression (likely due to a very long 5'UTR encompassing exons 1, 3, 4 et 5), it could have a weaker inhibitory activity on mRNA translation. Moreover, due to the N-terminal loss, this protein is surely ineffective on translation inhibition via direct RNA binding. Finally, this PDCD4 truncated form is probably a less efficient tumor suppressor and could define a new AML patient subgroup.