Vav1 is a crucial molecule in monocytic/macrophagic differentiation of myeloid leukemia cells

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Vav1 is physiologically expressed exclusively in haematopoietic cells, where it is a critical signal transducer in immune response. In addition to acting as a GEF involved in cytoskeleton rearrangement, Vav1 is an adapter molecule facilitating the interaction between other signaling proteins. Studies performed using knockout mice provided important insights into the function of Vav1 in both development and function of hematopoietic cells, including macrophages, in which it regulates adhesion, motility and migration speed.

In addition to modulate the acquisition of a mature phenotype by normal hematopoietic cells, Vav1 is a crucial molecule in the agonist-induced completion of the differentiation program of tumoral myeloid precursors. In particular, we have found that the over-expression of Vav1 promotes the overcoming of the differentiation blockade and enhances the ATRA-induced maturation of cells derived from acute promyelocytic leukemia (APL). We have also demonstrated that Vav1 modulates the expression level of the protein tool by means of which ATRA executes the differentiation program of tumoral myeloid precursors, possibly as part of transcriptional complexes.

Despite the multiple function played by Vav1 during the maturation to neutrophils of tumoral promyelocytes, none is known about a possible role for this protein in the differentiation of leukemic precursors to monocytes/macrophages. To address this issue, tumoral promyelocytes in which Vav1 was negatively modulated were induced to differentiate into monocytes/macrophages with PMA and monitored for their maturation level. Our data indicate that Vav1 is crucial for phenotypical differentiation of APL-derived cells to monocytes/macrophages, in terms of CD11b expression, adhesion capability and cell morphology. In addition, we have found that Vav1 and actin may cooperate in modulating nuclear morphology of PMA-treated adherent cells.

The obtained results allowed to establish that, in the same tumoral myeloid precursors, Vav1 may be recruited by different agonists as part of lineage-specific transduction machineries, highlighting the key role for this protein in the completion of the differentiation program of leukemic promyelocytes and suggesting Vav1 as a common target for the differentiation therapy of different subtypes of myeloid leukemias along the diverse hematopoietic lineages.

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Key words
Vav1, tumoral promyelocytes, PMA, myeloid differentiation, cell morphology