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Knockdown of SALL4 enhances all-trans retinoic acid (ATRA)-induced acute myeloid leukemia (AML) cell differentiation

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ATRA is a differentiation agent that revolutionized the treatment of a rare subtype of AML (APL, 5~10% of AML). However, it has not been useful for other subtypes of AML. Here, we explore the effect of SALL4, a newly identified stem cell factor, on cellular differentiation and growth arrest in the presence of ATRA treatment. Aberrant SALL4 protein expression has been found in all types of AML patient samples, while in normal blood cells, SALL4 expression is only restricted in the hematopoietic stem/progenitor cell (HSPC) populations. The reason is that SALL4 activation in AML may prevent the blast cells from differentiating and/or protect self-renewal that was normally seen in HSPCs. Indeed, in both APL and non-APL AML cells, a ~75% reduction of SALL4 levels caused significant upregulation of CD11B positive differentiated myeloid cells, along with a correspondingly increasing of apoptotic marker Annexin V activity. In these cells, co-treatment of ATRA induced further increment of cellular differentiation and growth arrest as judged by Wright-Giemsa staining, superoxide anion production and flow cytometry assays. In addition, SALL4 knockdown and ATRA exhibit a synergistic enhancement in impairing tumor growth in a mouse xenograft model of AML cells. Further molecular studies confirmed that SALL4 associates with retinoic acid receptor A (RARA) and modulates ATRA-regulated target genes. These results suggest that SALL4 functions asa component of the RAR co-repressor complex with an inhibitory effect on ATRA-induced cellular differentiation and that SALL4 plays a role in ATRA-mediated differentiation as an important aspect of leukemia therapy.

Biography

Jianchang Yang received his MD from XinJiang University of Medical Sciences in China and his PhD in Molecular Cardiology from Charite University Medicine (Berlin)-magna cum laude - in Germany. His research interests include the development of novel therapies for acute myeloid leukemia, using new approaches to killing leukemia stem cells; somatic cell reprogramming and the generation of patient-specific pluripotent progenitor cells for clinical therapies. He has published more than 23 papers in high impact journals.

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