Role of SET protein in Leukemogenesis and ATRA-induced Cell Differentiation in Acute Promyelocytic Leukemia (APL) Cells

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Introduction: Firstly identified as the SET-CAN fusion gene component of acute undifferentiated leukemia, SET acts as an endogenous inhibitor, whose activity is linked to the C subunit of phosphatase 2A. SET is overexpressed in chronic lymphocytic and chronic myeloid leukemia cells, decreasing PP2A activity. The role of SET in acute promyelocytic leukemia (APL) has not been established. **Objectives:** To understand SET involvement in both leukemogenesis of APL and ATRA-induced cell differentiation process. **Material and Methods:** The NB4 and NB4-R2 (APL) cells were treated with 1 µM ATRA (96 h), and SET localization was assessed by immunofluorescence and Western blotting of subcellular fractions. SET knockdown was performed using small hairpin RNA interference (shSET) and confirmed by Western blotting. NB4shSET and NB4-R2shSET cells were treated with ATRA and assayed for viability using propidium iodide, and for differentiation using anti-CD11bPE label/flow cytometry. The growth proliferation curve was performed by Trypan Blue exclusion method. **Results and Discussion:** SET protein was found overexpressed in APL; the SET protein was predominantly cytoplasmic, even after ATRA treatment. SET knockdown *per se* reduced cell proliferation in both APL cell lineages. However, the combination of SET knockdown with ATRA treatment in NB4 cells promoted a significant differentiation without inducing cell death, compared to treated control. In NB4-R2 cells, it was observed a trend to increase differentiation accompanied by cell death. Proteins involved in APL presented alterations, confirming cell differentiation and loss of SET function. The hnRNP K protein related with transcription and translation was modulated under shSET, suggesting a cross-talking between SET-hnRNPK in APL. Other studies are in progress to understand the mechanism. **Conclusions:** SET accumulation in APL cells impairs the ATRA action by blocking cell differentiation and contributes to leukemogenesis, conferring malignant characteristics like a high proliferation rate. Therefore, SET is a new potential target in APL treatment.

Palavra chave: Acute Promyelocytic Leukemia, SET, cell differentiation
Patrocínio: FAPESP, CEPID