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Combination of all-trans retinoic acid with tenascin-C derived peptide enhances neural differentiation of MYCN-amplified neuroblastoma cells

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Neuroblastoma is one of the common pediatric tumors. Among the neuroblastoma patients, high-risk group is characterized by amplification of the MYCN gene, which codes N-Myc protein. Excessively expressed N-Myc protein inhibits neuronal differentiation during normal development, which is a central aspect of neuroblastoma genesis. Despite mass-chemotherapy, the survival rate for high-risk neuroblastoma remains extremely low. Besides this low treatment efficacy, mass-chemotherapy has additional severe side effects, so-called "late effects", that occur many years after chemotherapy has ended. To solve this problem, differentiation therapy using retinoic acid and its derivatives has been expected as a mild chemotherapy with low risk of the late effects. However, the clinical outcome of differentiation therapy using retinoids including all-trans retinoic acid (ATRA) and its derivatives has not been sufficient due to the differentiation inhibition by over-expressed N-Myc protein. In the present study, we succeeded in synergistically accelerating the ATRA-induced neural differentiation of MYCN-amplified neuroblastoma cells by combining a peptide derived from tenascin-C, termed TNIIIA2, which has a potent ability to activate β1-integrins. Achievement of the high efficacy of neural differentiation was attributed to the induction of proteasome degradation of N-Myc protein by the combination of ATRA and TNIIIA2. Importantly, this enhanced differentiation was accompanied by a marked reduction of the malignant phenotype of neuroblastoma cells, and an in vivo experiment showed therapeutic potential of the combination therapy. These results provide a new insight into differentiation therapy for high-risk neuroblastoma based on N-Myc protein degradation.

Keywords: integrin-β1, tenascin-C, retinoic acid, N-Myc, neuroblastoma

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