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In human osteosarcoma 3AB-OS cancer stem cells let-7d seems to have the dual function of oncogene/tumor-suppressor miRNA

Riccardo Di Fiore, Rosa Drago-Ferrante, Francesca Pentimalli, Domenico Di Marzo, Iris Maria Forte, Daniela Carlisi, Anna De Blasio, Giovanni Tesoriere, Antonio Giordano, Renza Vento
Laboratory of Biochemistry, Department of Biological, Chemical and Pharmaceutical Sciences and Technologies, University of Palermo, Polyclinic, Palermo, Italy

Introduction: Osteosarcoma (OS), an aggressive tumor affecting adolescents, shows therapy resistance and recurrence which can depend on cancer stem cells (CSCs), the source for tissue renewal and hold malignant potential; thus, OS treatment requires their eradication. Here, using 3AB-OS CSCs previously obtained from the OS-MG63 cells, we focused on the role of let-7d in managing stemness properties of 3AB-OS CSCs.
Methods: 3AB-OS CSCs were stably transfected with pCDomH-plasmid, containing mir-let7-d, or empty vector as a control. Cell proliferation and viability were evaluated by EdU and Trypan blue assays, respectively. Sarcosphere and colony assays and wound healing and transwell invasion assays were performed to evaluate let-7d effects on self-renewal and migratory/invasive abilities of 3AB-OS cells, respectively. Publicly available databases were used to identify let-7d predicted target genes. RT-PCR and western blot analyses were employed to validate the targets of let-7d.
Results: We have found that let-7d-overexpression reduces cell proliferation, lowers CCND2 and E2F2, increases p21 and p27. Let-7d also decreases sarcosphere- and colony-forming ability and decreases Oct3/4, Sox2, Nanog, Lin28B and HMGA2. Moreover, let-7d induces mesenchymal-to-epithelium-transition, as shown by both N-Cadherin-E-cadherin-switch and vimentin decrease. This switch is accompanied by enhanced migratory/invasive capacities and by MMP9, CXCR4 and VersicanV1 increases. Resistance to serum starvation and chemotherapy, decrease in caspase-3 and increase in Bcl-2 were also observed.
Conclusions: This study shows that let-7d displays both suppressor and oncogenic functions, suggesting that, before prospecting new therapeutic strategies by let-7d use, it is urgent to better understand its functions.