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Identification of CD146 as a marker of tumor-propagating cells in human sarcomas leads to novel treatment opportunities

J. Wunder[1], J. Tang Yuning[2], Q. Wei[2], H. Whetstone[2], L. Ailles[3], G. Bader[2], B. Alman[4]

[1] *Mount Sinai Hospital, Toronto, Canada*

[2] *Hospital for Sick Children, Toronto, Canada*

[3] *Princess Margaret Hospital, Toronto, Canada*

[4] *Duke University, Durham, USA*

Tumor-propagating cells (TPCs) are believed to drive cancer initiation, progression and recurrence. These cells are characterized by enhanced tumorigenicity and self-renewal capacity. No cell surface markers for TPCs have been identified in primary human sarcomas. Therefore, our aim was to identify a robust marker that can isolate TPCs in primary human sarcomas and identify signaling pathways that are activated in TPCs, and which could be targeted for therapy. We previously used a functional dye-efflux assay to identify side population (SP) cells from sarcomas which have stem-like properties. Using a high throughput cell surface antigen screen, we identified markers highly enriched on the surface of side population (SP) cells from primary human osteosarcoma and undifferentiated pleomorphic sarcoma (UPS), which have TPC characteristics. In vivo serial transplantation assays were performed to test the tumorigenic potential of these markers. We found that CD146 is significantly enriched on the surface of SP cells, and serial transplantation assays of CD146+ cells from UPS and osteosarcoma in immunocompromised mice demonstrated that this cell population is highly tumorigenic, and can sustain tumor growth over multiple passages. Furthermore, we show that CD146+ and SP cells represent both distinct and overlapping populations of TPCs. Transcriptional profiling of CD146+ and SP cells revealed common activation of several signaling pathways including TGF-beta and Notch. Inhibition of the Notch pathway using a γ-secretase inhibitor significantly reduced tumor growth and self-renewal in both osteosarcoma and UPS, suggesting possible novel therapeutic options to reduce tumor recurrence for patients with high grade sarcomas.