UC San Diego
MOORES CANCER CENTER
An NCI-designated Comprehensive Cancer Center

American Cancer Society – Institutional Research Grants 2014

"Integrin αvβ3 drives an EMT-independent role for slug in cancer stemness"

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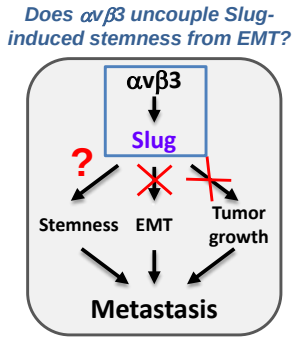
Breast cancer stem cells (CSCs) promote tumor recurrence and metastasis and are associated with disease progression in breast cancer patients. Increased cell survival and self-renewal make these cells resistant to therapy and more likely to contribute to aggressive disease. Integrins act as key cell surface receptors regulating *adhesion-dependent* functions critical for CSCs and cancer progression. We previously reported in *Nature Medicine* that the integrin αvβ3, in particular, can function in a non-canonical *anchorage-independent* manner to drive breast cancer progression and metastasis. We now report in *Nature Cell Biology* that anchorage-independence is one of many CSC properties associated with αvβ3 expression in human tumor cells. These findings prompted us to ask whether αvβ3's role in breast CSCs might be derived from a conserved mechanism employed by adult mammary stem cells (MaSCs).

Since MaSCs share a number of properties with breast CSCs, and may act as the cells-of-origin for aggressive breast cancers, we investigated a potential normal physiological role for αvβ3 in the adult mammary gland. This approach resulted in the discovery that αvβ3 is critical for Slug activation, MaSC expansion and mammary remodeling during pregnancy, recently published in *Developmental Cell*. Although the transcription factor Slug is best known for its role in epithelial-mesenchymal transformation (EMT), recent studies support a unique function for Slug as a master regulator of the MaSC state. We found that β3 was necessary for Slug expression in MaSCs in a manner independent of EMT or cell proliferation. In Preliminary Results we now demonstrate in human breast cancer cells that αvβ3 is necessary and sufficient for Slug activation and tumor stemness, but dispensable for primary tumor growth or EMT. **Therefore, I propose to test the hypothesis that αvβ3 selectively drives an atypical function for Slug in promoting breast cancer stemness and metastasis.**



The following innovative, yet feasible studies will test the relevance of this pathway in breast cancer:

Aim1: Explore whether Slug is required for αvβ3-mediated stem-like properties in human breast cancer cells. *We will examine how Slug loss- or gain-of-function impacts αvβ3-induced stemness in vitro (anchorage-independent survival, colony formation, and self-renewal).*

Aim2: Determine if Slug contributes to αvβ3-induced stemness and/or metastasis *in vivo*. *We will investigate whether αvβ3 influences Slug's role in tumor initiation, in contrast to primary tumor growth, and whether this may be related to Slug's ability to promote metastasis.*

The contribution of stemness to metastatic disease has proved difficult to determine since many molecules have additional functions affecting tumor growth or EMT. Our recent studies have provided us with unique insight into a bona fide adult MaSC pathway necessary for mammary gland remodeling, allowing us to examine a potential role for this pathway in tumor cell stemness and metastatic disease, independent of EMT or proliferation. Future studies will elucidate the signaling mechanisms responsible for αvβ3/Slug-mediated stemness properties, with the ultimate goal of identifying new therapeutic targets in CSCs that may prevent tumor recurrence and metastasis. Additionally, data generated under this award will serve as the basis for additional funding including NIH R01 support.