UC San Diego
MOORES CANCER CENTER

2021 Gleiberman Head and Neck Cancer Center Pilot Grant

Targeting Invadopodia to Inhibit Head and Neck Cancer Metastasis

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Scientific Abstract:

Head and neck squamous cell carcinoma (HNSCC) is the sixth leading cancer by incidence worldwide. While localized HNSCCs have 70-90% cure rates, the median survival time for metastatic HNSCCs is only 5-9 months. In order to invade the surrounding tissues and form metastasis, HNSCC cells concentrate various matrix proteases at specialized actin-based membrane protrusions termed invadopodia to carry out focal extracellular matrix (ECM) degradation. The ability to concentrate various matrix proteases at focal points for ECM degradation differentiates invadopodia from other actin-based structures. This unique character and the important role of invadopodia in HNSCC invasion and metastasis present these structure as excellent targets for anti-metastasis therapy without affecting normal actin dynamics.
However, molecular components and mechanisms that drive invadopodia formation and function are not well understood. Given the tiny size and highly dynamic nature of invadopodia, studying the proteome of these structure is technically challenging and no effective methods are available to biochemically isolate them from other membrane components. To address this question, our proposed research aims to use a new APEX2-mediated proximity labeling proteomics approach to identify novel proteins that localize and regulate invadopodia formation and function in HNSCC cells. We will next characterize the molecular functions of these proteins at invadopodia and test whether inhibiting the functions of these proteins could block HNSCC local invasion and metastasis in mice and in human HNSCC tumor samples. We hope that our research will yield mechanistic insight into invadopodia regulation and identify effective molecular targets for anti-metastasis therapy in oral HNSCC.

Lay Abstract:

While localized head and neck squamous cell carcinoma (HNSCC) have 70-90% cure rates, the median survival for metastatic HNSCCs is only 5-9 months. Therefore, there are urgent unmet needs to provide better prognostic markers for metastatic disease stratification and to develop effective therapies to prevent HNSCC invasion and metastasis.
Degradation of extracellular matrix (ECM) is essential for cancer cell invasion and metastasis. Proteolytic activity is associated with increased metastasis and poor clinical outcome in HNSCC. However, numerous MMP inhibitors have failed in clinical trials for HNSCCs partially due to the anti-tumorigenic roles of MMPs in immune cells. Recent research shows that HNSCC tumor cells concentrate various matrix proteases, including MMPs, at specialized membrane protrusions termed invadopodia to carry out focal ECM degradation. The ability to concentrate proteases at focal points for ECM degradation differentiates invadopodia from other actin-based protrusions. This unique character presents a regulatory program to target invadopodia for anti-metastatic HNSCC therapy without affecting actin dynamics in normal cells and causing overall toxicity. However, the molecular mechanisms that regulate invadopodia formation

and function in metastatic HNSCC tumor cells remains largely unexplored.

In this pilot project, we aim to use an innovative and new technology to identify novel proteins that promote matrix degradation and HNSCC tumor invasion and metastasis. These candidates could serve as prognosis and therapeutic targets to treat HNSCC metastatic patients and/or improve their long-term survival. The ultimate goal of this pilot project is to understand how invadopodia are assembled and regulated to degrade matrix and drive HNSCC invasion and metastasis.