Role of Non-canonical Wnt5a Signaling in Metastatic Oral Cavity Squamous Cell Carcinoma

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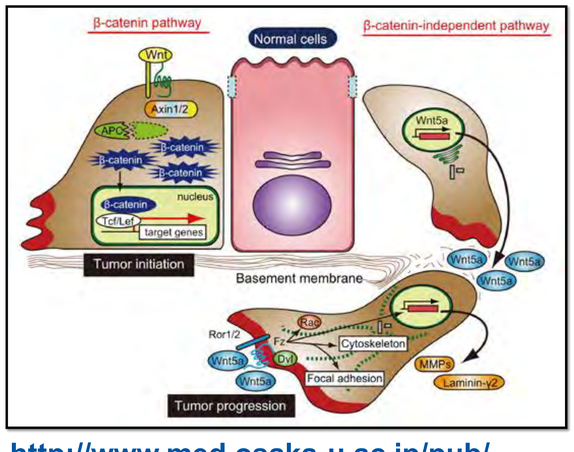
Background

- Lymph node metastases is the primary determinant of stage, recurrence risk, and survival in head and neck squamous cell carcinoma (HNSCC).
- The underlying mechanisms driving lymph node spread are unknown.
- One proposed mechanism is the migration of "tumor initiating cells" or TICs from the primary site to the lymph node metastatic niche.
- Microenvironment microarrays are a novel platform for evaluating which growth factors and extracellular matrix proteins lead to cell adhesion, survival and TIC marker expression.
- The Wnt pathway is intimately involved in niche interactions and migration through the non-canonical planar cell polarity pathway.



http://www.med.osaka-u.ac.jp/pub/molbiobc/researches_e.html

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Microenvironment Microarrays (MEMAs)

- HNSCC cell lines UMSCC-10A, 10B, 22A, and 22B were incubated on microarrays for 5 days and stained with TIC marker CD44.

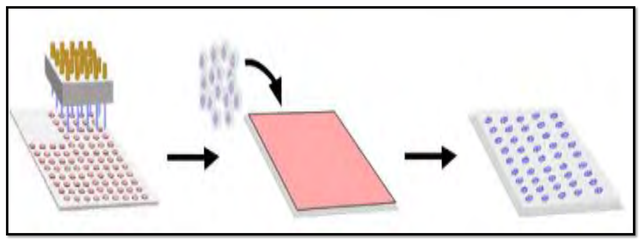

Figure 1. Proteins are spotted in combinatorial format on the array located in a multi-well cell culture dish. Cells are incubated over the array and preferentially bind to certain spots.

Wnt5a
Wnt10b
SDF1α
EGF
Jagged2

Table 1. Proteins leading to increased CD44 expression in MEMA screen in both primary (A) and lymph node (B) lines.

Wnt 5a Validation Patient Samples

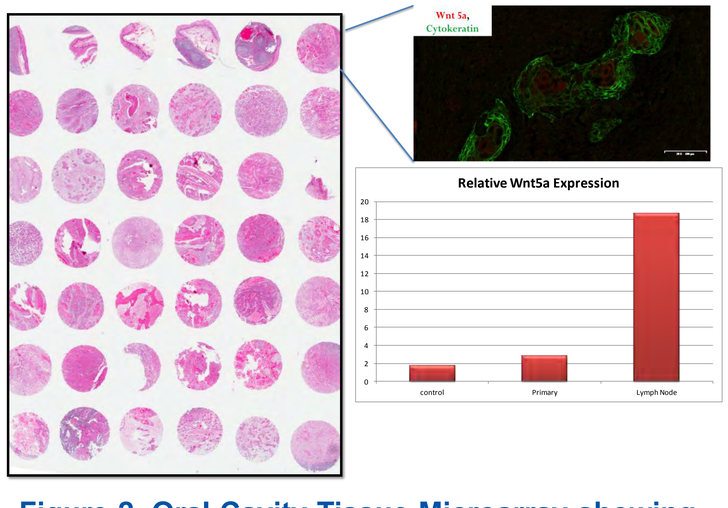

Figure 2. Oral Cavity Tissue Microarray showing increased Wnt5a in lymph nodes compared to primary samples and sleep apnea controls.

Wnt 5a Validation In Vitro

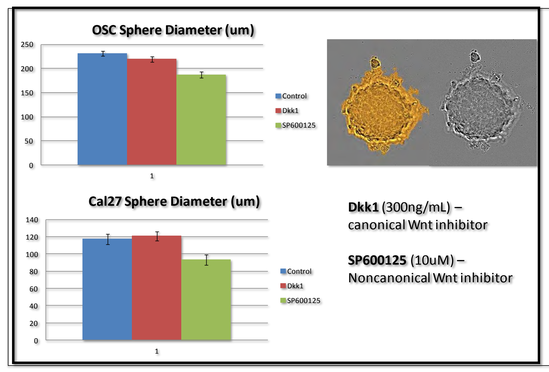

Figure 3. Non-canonical inhibitor of the Jnk pathway inhibits sphere formation in oral cavity cell lines.

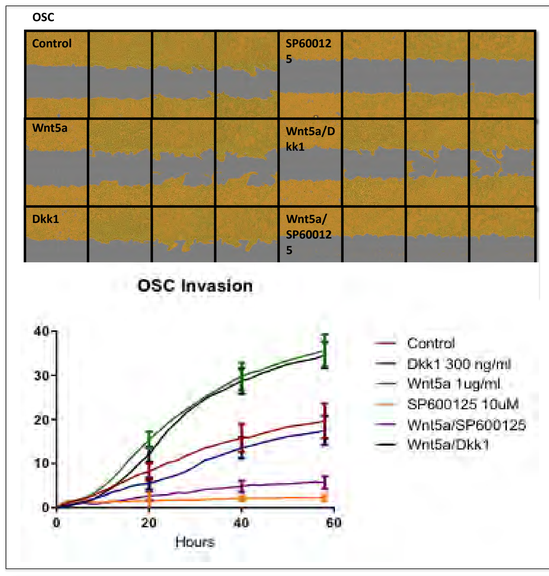

Figure 4. Non-canonical inhibitor of the Jnk pathway inhibits migration in oral cavity cell lines.

Conclusions Future Directions

- MEMAs can yield interesting targets involved in microenvironment niche interactions.
- Inhibition of niche proteins may lead to more effective therapy.
- Non-canonical Wnt5a ligand is overexpressed in HNSCC lymph nodes .
- Non-canonical Jnk inhibitor SP600125 inhibits migration and tumorigenicity indicating this pathway may be a good target for future preclinical studies.
- Ongoing in vitro assays will clarify the interaction between Wnt5a and Jnk pathways and the role of Wnt5a in migration.