The Role of Inflammation in Epithelial-Mesenchymal Transition in Oral Squamous Cell Carcinoma: Literature Review, Preliminary Data, and Proposal of Experiments

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Introduction & Objectives

The epithelial-mesenchymal transition (EMT) is a trans-differentiation process of epithelial cells into motile mesenchymal cells. It plays an integral role in embryonic development, wound healing, and cancer progression. During EMT, epithelial cells lose their cellular polarity due to the loss of intercellular adhesion and acquire migratory and invasive characteristics associated with mesenchymal cells. EMT is tightly regulated by a number of distinct molecular processes which allow its initiation and progression to completion. These processes include activation of transcription factors, expression of specific cell-surface proteins, reorganization and expression of cytoskeletal proteins, production of extracellular matrix-degrading enzymes, and changes in the expression of specific microRNAs. In many cases, the involved factors are also used as biomarkers to demonstrate the passage of a cell through an EMT.

The role of chronic inflammation in cancer development was first described in 1863, and has since been linked to tissue invasion and metastasis. Inflammatory cytokines produced by local cells, tumor-associated macrophages in particular, have long been known to positively correlate to metastatic occurrences. In addition, accumulating evidence has suggested that certain types of cancer cells directly respond to bacterial virulence factors by synthesizing molecules that further promote invasion and/or metastasis.

Oral squamous cell carcinoma (OSCC) is the most common malignancy affecting the oral and maxillofacial complex. Common risk factors, such as cigarette smoking, alcohol consumption, and oral microbiota, have been linked to the development of OSCC. It is well known that the gut microbiota release substances that affect EMT. Therefore, the oral microbiota potentially promote EMT in OSCC in a similar manner.

In this study, we present current knowledge on EMT, including its regulatory genes and their target proteins, and the role of chronic inflammation associated with OSCC in initiating EMT. We also discuss the preliminary data and suggest potential future experiments/future research directions.

Literature Review

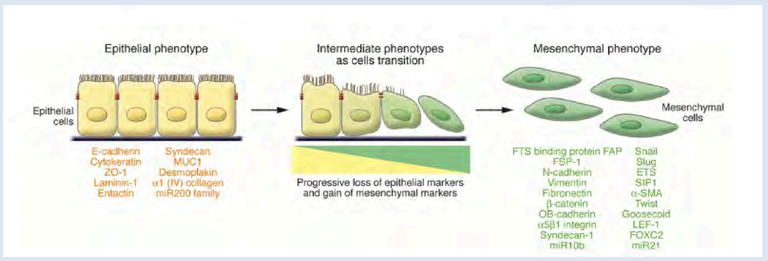

Figure 1. EMT. An EMT involves a functional transition of polarized epithelial cells into mobile and ECM component–secreting mesenchymal cells. The epithelial and mesenchymal cell markers commonly used by EMT researchers are listed.

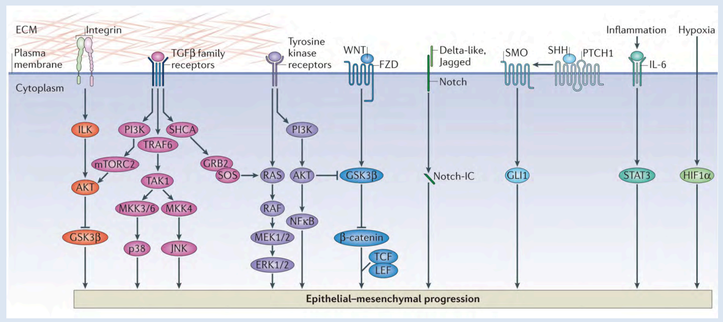

Figure 4. Signaling pathways involved in EMT.

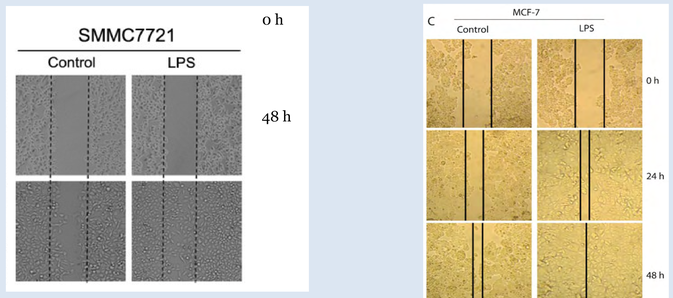

Figure 2. Enhanced migration and invasion of breast (MCF-7) and hepatocellular (SMMC7721) cancer cell lines in response to lipopolysaccharide (LPS). Wound-healing assay to observe changes in SMMC7721 and MCF-7 cells invasion after LPS stimulation for 48 h.

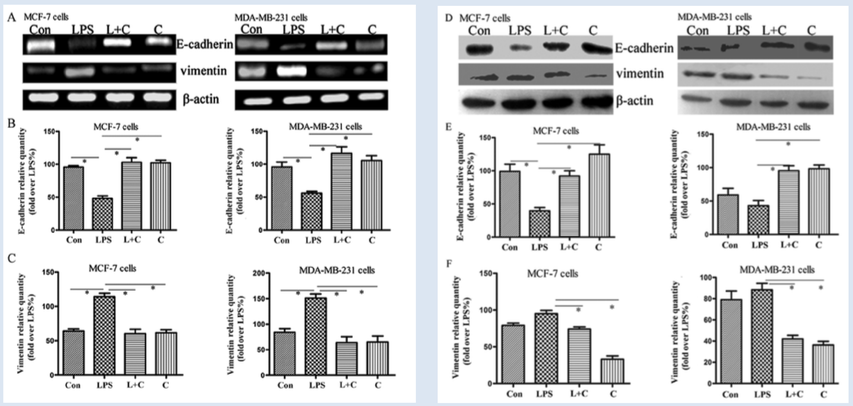

Figure 3. Brest cancer cells down-regulated E-cadherin mRNA (A-C) and protein and up-regulated vimentin mRNA and protein (D-F) in response to LPS. The mRNA expression levels of E-cadherin and vimentin in MCF-7 and MDA-MB-231 cells were determined by RT-PCR. The protein expression of E-cadherin and vimentin in MCF-7 and MDA-MB-231 cells was determined using western blot analysis.

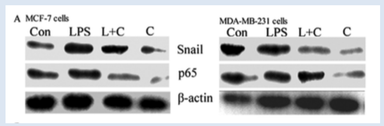

Figure 4. Brest cancer cells up-regulated NF-κB p65 subunit and Snail in response to LPS. Western blot analysis of the protein expression of the NF-κB p65 subunit and Snail in MCF-7 and MDA-MB-231 cells after treatment for 24 h.

Preliminary Data

- OSCC cell lines (HSC-2, HSC-3, and HSC-4) tested expressed toll-like receptor 4 (TLR4, Data not shown).
- Initial wound-healing assay with HSC-3 cells revealed that LPS enhanced migration of cells in a dose dependent manner (Figure 5).

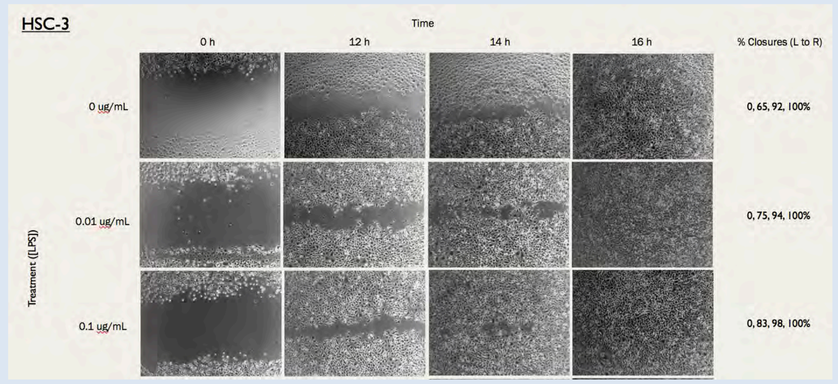

Figure 2. LPS enhanced migration of breast HSC-3 cells in a dose dependent manner. Wound-healing assay to observe changes in HSC-3cells invasion after graded concentration of LPS stimulation for 16 h.

Future Research Directions

Aim: **To test the hypothesis that LPS enhances EMT in OSCC (HSC-2, HSC-3 and HSC-4).**

- Expression of E-cadherin and N-cadherin on OSCC in response to LPS with or without TLR4 neutralizing antibody.
- Repeat migration assay.
- Characterization of signaling pathways involved in LPS-driven OSCC EMT.
  - NFκB
  - Snail
  - JAK/STAT3

We are also growing other OSCC, OECM-1 cells, and will characterize the phenotypic analysis of these cells related to EMT.

References

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