p38 MAPK Mediates Epithelial-Mesenchymal Transition by Regulating p38IP and Snail in Head and Neck Squamous Cell Carcinoma.

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Education Objective
At the conclusion of this presentation, the participants should be able to recognize the role of p38-p38 signaling in the epithelial-to-mesenchymal transition (EMT) in head and neck squamous cell carcinoma (HNSCC).

Background
In the present study, we investigated the role of p38-p38 signaling in the epithelial-to-mesenchymal transition EMT in HNSCC.

Study Design & Methods
Quantitative RT-PCR, western blot analysis, immunohistochemical staining of human HNSCC tissue sections were used.

Results
p38 inhibitor treated and p38 shRNA HNSCC cell lines show a decrease in lysine negative protein expression in a p38 dependent manner. In clinical HNSCC samples, p38 interacting protein (p38IP) is significantly increased compared to adjacent normal tissue. An inverse correlation was observed between p38IP and Snail expression in HNSCC patient specimens and cell lines. p38 knockdown decreases Snail expression. Knockdown of p38IP increased E-cadherin expression, and decreased Snail expression in HNSCC cell lines. The induction of p38IP is increased in HNSCC patient tumors, compared to adjacent normal tissue.

Figure 1.

Discussion
Metastasis is a primary cause of mortality in many cancers, including HNSCC. Understanding the molecular mechanisms that mediate EMT may enable identification of novel therapeutic targets. Previous work has demonstrated the loss of E-cadherin gene expression, which is the hallmark of EMT, is due to up-regulation of Snail and other transcription factors that directly repress E-cadherin expression.

To determine the role of p38 in EMT, we used shRNA to inhibit p38, and knocked down expression of p38 using mRNA in HNSCC cell lines. p38 inhibitor SB203580 treated, and p38 shRNA HNSCC cell lines demonstrated a significant up regulation in E-cadherin mRNA and a decrease in the mRNA expression of the transcriptional repressor Snail. The addition of SB203580 in HNSCC cell lines led to an up regulation of other epithelial markers (E-cad), and a down regulation in mesenchymal markers (vimentin). Interestingly, p38 knockout HNSCC cell lines show a less invasive and more epithelial phenotype in a 3-dimensional sphere model.

Intriguingly, we found that p38IP, a histone acetyltransferase subunit downstream of p38 signaling, is dysregulated in HNSCC cell lines and patient samples. p38IP has been reported to promote the function of the histone acetyltransferase enzyme GCN5 in the STAGA complex in vivo. [2]. Our results confirm the published literature [1]. In the present study, we investigated the role of p38-p38IP signaling in the regulation of EMT in human HNSCC.

HNSCC. Furthermore, in human squamous cell carcinoma we confirm a reciprocal relationship between p33 and STAGA. These findings suggest that therapies targeting the p38-p38IP pathway may diminish the propensity for tumor metastasis in HNSCC by blocking the activation of EMT. In this newly defined pathway for transcriptional regulation of E-cadherin in HNSCC may have important implications for chemoprevention as well as therapies utilizing p38 inhibitors in combination with other agents.

Conclusion
We identified a novel transcriptional regulation of E-cadherin in HNSCC. Furthermore, in human squamous cell carcinoma we confirm a reciprocal relationship between p33 and STAGA. These findings suggest that therapies targeting the p38-p38IP pathway may diminish the propensity for tumor metastasis in HNSCC by blocking the activation of EMT. In this newly defined pathway for transcriptional regulation of E-cadherin in HNSCC may have important implications for chemoprevention as well as therapies utilizing p38 inhibitors in combination with other agents.

References

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