The Interaction of Cancer Associated Fibroblasts and Peri-Tumoral Inflammatory Response in Oral Cavity Squamous Cell Carcinoma

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Abstract

Background: The tumour-host interface is a critical location in understanding the interaction of the immune system and progressing tumor.

Objectives: To determine the relationship between peri-tumoral inflammation and α-SMA, a surrogate marker for cancer associated fibroblasts (CAFs).

Design: Retrospective case series of subjects who had undergone surgical extirpation for oral cavity squamous cell carcinoma (OCSCC) with histopathological evaluation of the invasive front.

Results: Subjects who exhibited a peri-tumoral inflammatory response had lower stromal α-SMA expression in CAFs.

Conclusion: The stroma mediates the peri-tumoral inflammatory response.

Introduction

- The interface between the tumor and the host is a critical location that could be used to understand the interaction of the immune system and an invasive tumor.
- Cancer associated fibroblasts (CAFs) have been recognized as crucial elements of the epithelial to mesenchymal transition, and metastatic potential of the tumor.
- α-SMA is a marker of CAFs, and can therefore be used in the assessment of the tumor microenvironment.

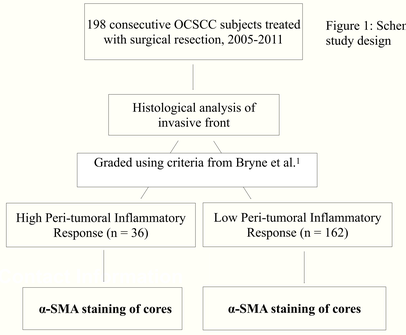


Figure 1: Schema of the study design

Methods

- Retrospective case series of subjects who had undergone surgical extirpation OCSCC between 2005 – 2011.
- Histopathological analysis at the invasive front and specimens were graded to characterize the inflammatory response at the invasive front according to the Bryne et al. criteria[1].
- A tissue micro array from the same tissue as the invasive front was used to determine if α-SMA was associated with the inflammatory response.
- Tumor and stromal areas were manually marked and analyzed on each core to calculate the percent of CAF's that were positive for α-SMA.

Results

- 198 subjects were included in the study.
- Median follow up was 5.8 years (range 0.1-11.9 years).
- The presence of a peri-tumoral inflammatory response at the invasive front was observed in 18.2% (n= 36) of patients.
- The patients who exhibited a peri-tumoral inflammatory response had lower stromal α-SMA expression and density in cancer associated fibroblasts (Figure 2, 8.3 vs 20.3, $p < 0.001$).

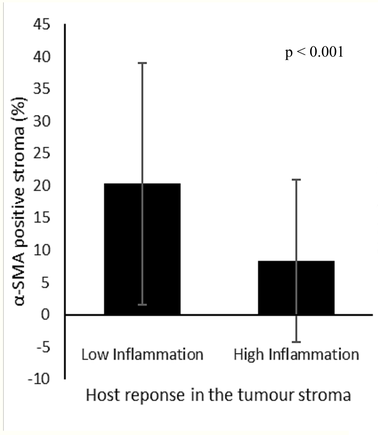


Figure 2. There was a decreased α-SMA positive tumor stroma in patients with high peri-tumoral inflammation compared to those with low peri-tumoral inflammation.

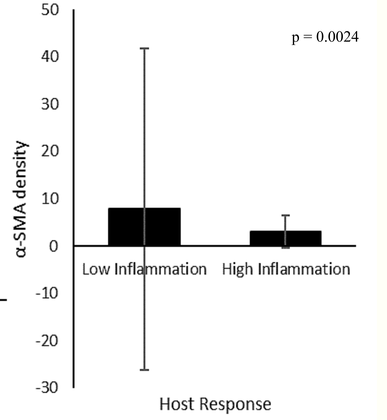


Figure 3. There was a significantly lower density of α-SMA in the tumour stroma of the high peri-tumoral inflammation group compared to the low peri-tumoral inflammation group.

Discussion

- The results of this study indicate that tumours expressing markers of cancer associated fibroblasts (α-SMA) may suppress the host inflammatory response.
- Our results also suggest that the stroma plays a significant role in mediating the host inflammatory response.
- Peri-tumoral inflammatory response along the invasive front is associated with improved recurrence free survival in other studies[2]
- Tumors expressing markers of EMT in concert with stromal factors may suppress the inflammatory response leading to disease progression.
- Assessment of the peri-tumoral inflammatory response may allow for risk-stratification and prediction of more aggressive disease.

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Future Direction

- Evaluation of how peri-tumoral infiltrate and stromal α-SMA impact clinical outcomes.
- Additional study of interaction between stroma and tumor.

Conclusions

- Cancer associated fibroblasts in the stroma may play a significant role in reducing the host inflammatory response to the tumor at the invasive front.

References

1. Bryne M, Koppang HS, Lilleng R, Stene T, Bang G, Dabelsteen E. New malignancy grading is a better prognostic indicator than Broders' grading in oral squamous cell carcinomas. *J Oral Pathol Med*. 1989;18(8):432-437. doi:10.1111/j.1600-0714.1989.tb01339.x

2. Knops AM, South A, Rodeck U, et al. Cancer-Associated Fibroblast Density, Prognostic Characteristics, and Recurrence in Head and Neck Squamous Cell Carcinoma: A Meta-Analysis. *Front Oncol*. 2020;10(November):1-11. doi:10.3389/fonc.2020.565306

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