The immune landscape of HPV+ and HPV- head and neck cancers: a comparison of immune infiltration

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The Tumor Immune Microenvironment of Head and Neck Cancers

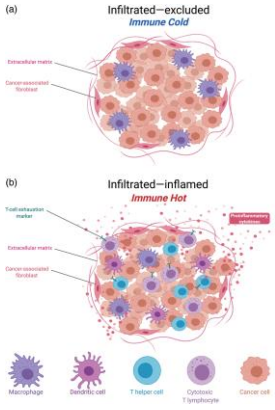
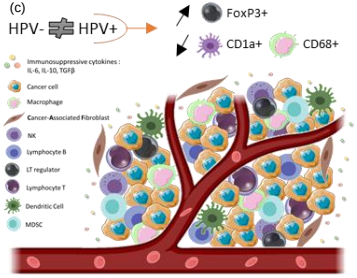


Figure 1: The tumor immune microenvironment (TIME) can be divided into two broad classes based on their immune contexture. The tumor core of infiltrated–excluded environments lack cytotoxic T lymphocyte (CTL) infiltration and their secreted proinflammatory mediators but contain tumor-associated macrophages (a). In contrast, the environments of infiltrated–inflamed tumors are characterized by high infiltration with CTLs that express elevated levels of T-cell exhaustion markers and high levels of proinflammatory mediators (b) (Gameiro et al, 2021). The TIME of HPV+ head and neck cancers (HNC) has a distinct immune composition to that of its HPV- counterpart. HPV+ TIME is immunologically "hot", with more immune infiltration, higher levels of T-cells and decreased levels of macrophage infiltration (c).



Patients and Methods

Table 1. Patient population characteristics related to p16 status

Variables	Number of p16 negative cases (n=31)	Number of p16 positive cases (n=29)
Age (years)		
Median (range)	62(42-79)	64 (44-89)
Recurrence (RFS) (months)	7 (1-84)	14 (1-106)
Median (range)	17	9
Yes	14	18
No	0	2
Unknown		
Overall Survival (OS) (months)	10 (1-97)	14 (1-106)
Median (range)	14	17
Alive	17	11
Dead	0	1
Unknown		
Gender		
Male	21	22
Female	10	7
Anatomical site		
Oral cavity	17	5
Oropharynx	4	15
Larynx	9	7
Hypopharynx	1	1
Nasopharynx	0	1
Tumor stage		
I-II	23	12
III-IV	7	11
Unknown	1	6
Histological grade		
Undifferentiated	1	5
Poorly differentiated	7	11
Moderately differentiated	8	3
Well differentiated	15	4
Unknown	0	6
Tumor invasion		
Yes	26	21
No	5	5
Unknown	0	3
Risk factors		
Tobacco		
Smoker	29	22
Non-smoker	2	7
Alcohol		
Drinker	20	17
Non-drinker	11	12

N= **60 tumors** targeted by immunohistochemistry for:

- **p16**
- **CD8** → cytotoxic T-lymphocytes
- **FoxP3** → regulatory T-lymphocytes
- **CD68** → Macrophages
- **CD80** → M1 macrophages
- **CD163** → M2 macrophages
- **CD1a** → Langerhans cells

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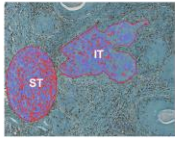


Impact of p16 positivity on immune cells recruitment in H&N cancers

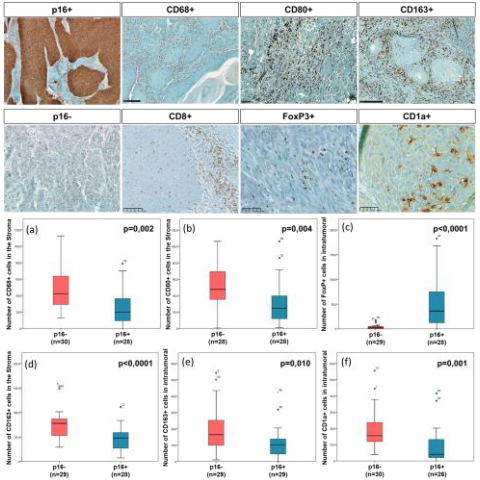
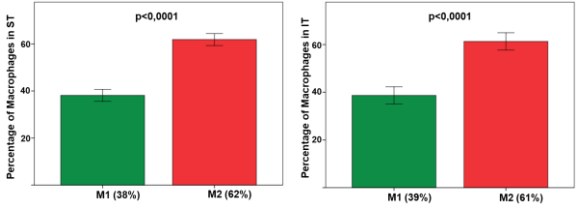


Figure 2: Based on the mean counts, we performed Mann-Whitney tests to compare the differential infiltration of each immune cell type between p16-positive and p16-negative patients. First, in the stromal compartment, statistical analyzes revealed a significant decrease in the density of CD68+ (a), CD80+ (b) and CD163+ (d) macrophages within p16+ tumors in comparison to p16- tumors. Conversely, FoxP3+ Treg lymphocytes were significantly more recruited by p16+ tumors in intratumoral area compared to p16- tumors (c). Similarly, CD1a+ Langerhans cells and CD163+ M2 macrophages were significantly less present in the intratumoral compartment of p16+ tumors compared to p16- tumors (e) (f). In summary, we observed a drop in the recruitment of cells related to the innate immune system in p16+ tumors, in parallel with a massive recruitment of lymphocyte cells that depend on the adaptive immune system

Which type of macrophages are most found in HNCs?



Considering the high infiltration of macrophages in head and neck cancers as reported in the literature, and their association with a worse prognosis in patients, we investigated their phenotypes by targeting M1 and M2 macrophages using specific phenotypic markers such as CD80 and CD163, respectively. Secondly, we calculated their proportion in both compartments and we observed that more than 60% of stained macrophages are tumor associated macrophages (TAMs / M2) which play essential roles in tumorigenesis. They are implicated in angiogenesis, in migration, invasion and in immunosuppression (Aras et al, 2017; Lechien et al, 2020). These findings support the implication of M2 macrophages particularly in HPV- head and neck carcinogenesis.

Conclusion

There is clear evidence that the immune landscape of HPV+ HNSCC represents a T-cell-inflamed phenotype that is very different from HPV− HNSCC. The improved patient outcomes generally associated with HPV+ HNSCC also suggests that deintensification of traditional highly-toxic therapies to reduce treatment-induced sequelae may also warrant investigation.

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