Histopathological characterization of esophageal cancers and potential role of high-risk HPV infections

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1) Background

In the esophagus, two main cancer subtypes can be diagnosed: adenocarcinoma (within the gastro-esophageal junction) and squamous cell carcinoma (in the upper part). Interestingly, these two cancers are found in both uterine cervix and anal canal where the etiological role of HPV is largely described in the literature. In contrast, the link "HPV-cancer" in esophageal cancers is still very controversial.

2) Aim

The main goal of this project is to characterize histopathologically the esophageal malignancies and to determine the potential role of carcinogenic HPV infection in the development of a substantial proportion of these latter.

3) Methods

In collaboration with both the local biobank and Bordet institute, we first collected a large cohort of adenocarcinoma (n=100) and squamous cell carcinoma (n=77). We analyzed the HPV status of each specimen by genotyping. The viral transcriptomic activity has then been determined using RT-PCR and RNAscope. This procedure allowed us to classify all samples into three categories: HPV-negative, HPV DNA+/RNA- and HPV DNA+/RNA+ samples. These three sub-groups were finally compared with each other according to various characteristics: p53 status, proliferative index (Ki67), $p16^{ink4a}$ and Keratin 7 positivity as well as the PD1+ andCD8+ cell densities.

4) Results

Among 64 esophageal adenocarcinoma, 23 samples were negative for HPV (23/64, 36%) and 41 displayed a positive DNA signal (41/64, 64%). The most common genotype was HPV16 (34/41, 83%), followed by HPV18 (19/41, 46%). Regarding the viral transcriptional activity, 17 tissue specimens were HPV16 or 18 RNA positive (17/37, 46%). When the three categories (HPV negative, HPV DNA+/RNA- and HPV DNA+/RNA+) were compared with each other, no significant difference was observed regarding the proliferation index, p53 status, $p16^{ink4a}$ and Keratin 7 positivity as well as PD1+ and CD8+ cell density. Regarding the clinical data of patients, HPV status doesn't seem to affect overall survival either. The characterization of the last 36 specimens is ongoing. Regarding the cohort of esophageal squamous cell carcinoma, only 7 samples were positive for DNA HPV and displayed a viral transcriptional activity (7/77, 10%). Although these results are

preliminary, this category (HPV DNA+/RNA+) seems to have a higher cellular proliferation, strongly express $p16^{ink4a}$ and have a wild-type p53 status.

5) Conclusion

Overall, more than half of esophageal adenocarcinoma samples have been shown to be positive for HPV infection but a transcriptionally active infection was encountered in a relatively modest proportion of samples. In addition, HPV status doesn't seem to affect neither the histopathological features of adenocarcinoma nor the patient survival. The same characterization is currently ongoing on a larger number of both adenocarcinoma and squamous neoplams.

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