Circulating plasma and salivary extracellular vesicles proteomes indicate prognostic signature in oral cancer

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Oral squamous cell carcinoma (OSCC) is the most common type of head and neck malignant tumor and the fifth most frequent cancer in Brazil with high prevalence and morbidity. Research efforts have focused on the discovery of signature prognostic markers using minimally invasive liquid biopsy to guide the decision of the appropriate treatment for OSCC patients. In particular, extracellular vesicles (EVs) are important mediators in the intercellular communication with critical role in the establishment of pre-metastatic niche. In this study, we compared the proteome of circulating EVs from saliva (n = 32) and plasma (n = 31) between patients with (N+) or without lymph node metastasis (N0) to investigate metastasis signature in EVs. The majority of the 1,071 and 1,414 proteins quantified in salivary and plasma EVs were associated with the enrichment of antigen processing and cell-cell adhesion biological processes, and platelet degranulation and complement activation, respectively. From the 49 salivary EV proteins with difference in abundance between N0 and N+ samples ($p<0.05$, Student's t test), 46 were able to stratify these patients (AUC>70%) using logistic regression (LR) model or random forest (RF). Likewise, 130 proteins were differential between the plasma EVs proteomes, from which 114 were able to classify these patients in LR and RF models. Moreover, nearly 20 proteins from each dataset were associated to clinicopathological features (Linear regression, P value < 0.05, R < ?0.7 or 0.7 < R and $R2 > 0.5$) and were further verified using parallel reaction monitoring in independent cohorts (salivary EVs n= 20N+ and 7 N0, plasma EVs n= 6N0 and 11N+; 54 proteins and 223 proteotypic peptides). In conclusion, salivary and plasma EV proteins are promising as prognosis signature markers to the management of OSCC patients.

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