

HPV⁺ Head and Neck Squamous Cell Carcinoma-Derived Exosomes Mediate Neutrophil Attraction via Activation of Fibroblasts in the Tumor Microenvironment

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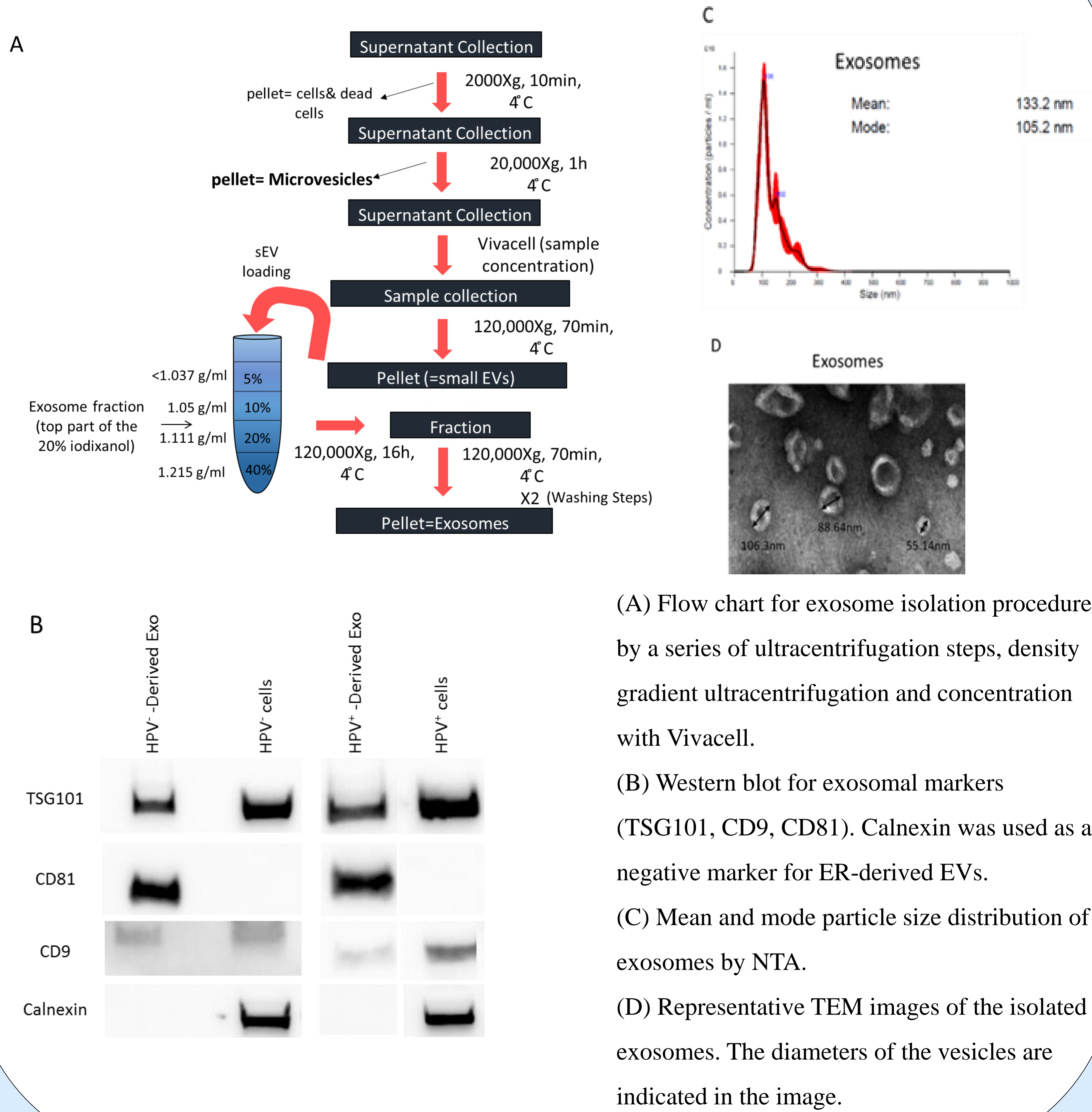
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Abstract

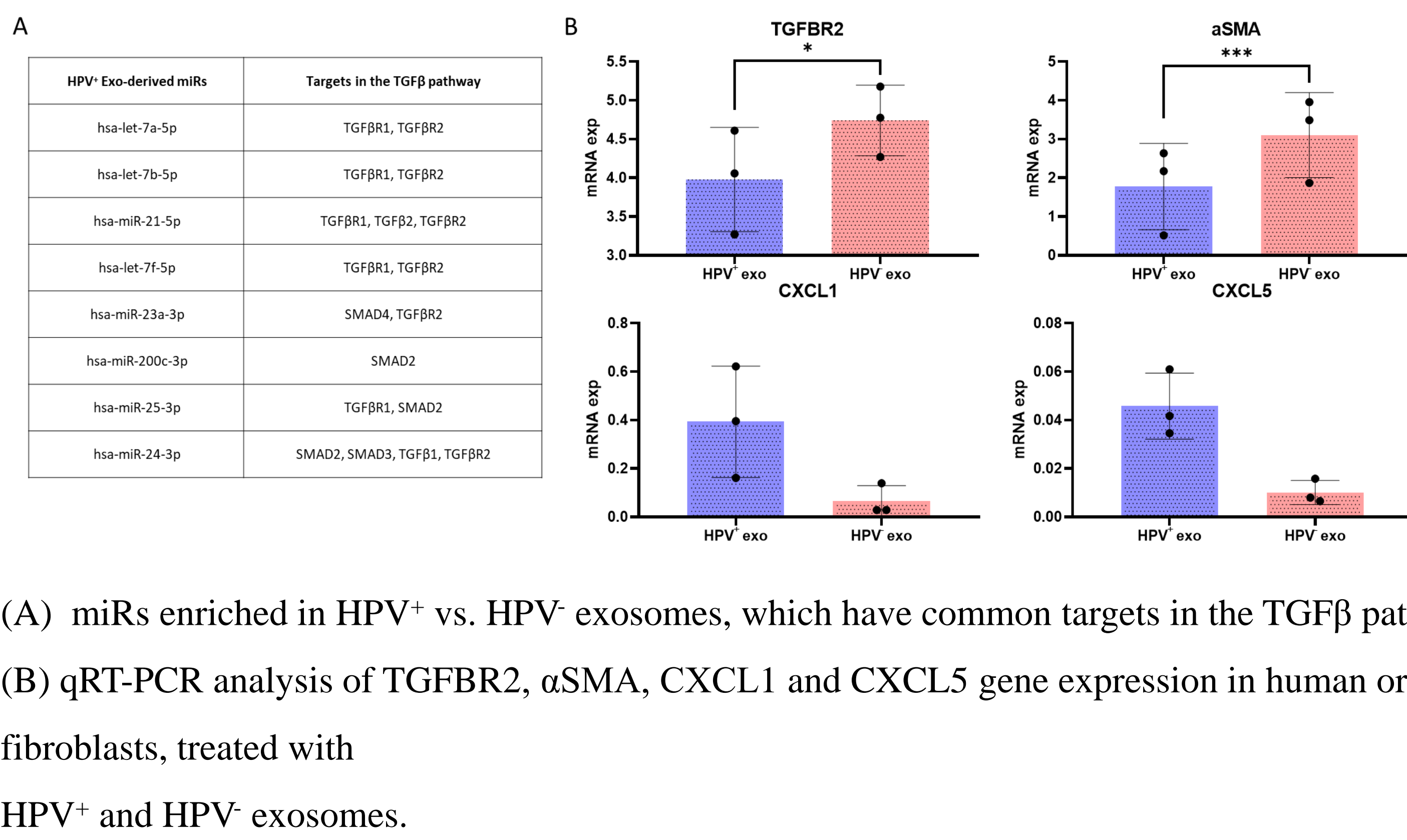
Head and Neck Cancer Squamous Cell Carcinoma (HNSCC) accounts for more than 90% of the cancer of the head and neck. Human Papilloma Virus (HPV) infection has been implicated in the pathogenesis of 25% HNSCC cases in the United States. The impact HPV has on the tumor microenvironment (TME) is in its infancy. Cancer-Associated Fibroblasts (CAFs) in the TME play a major role in tumor progression by mediating inflammation and ECM modifications. Understanding pathways of communication between tumor cells and fibroblasts is an important step in deciphering the challenging phenomenon of cancer progression. To address this question, we analyzed the miRNA content of HPV⁺ and HPV⁻ HNSCC-derived exosomes, and tested their impact on fibroblast activation. We found that HPV⁺ and HPV⁻ exosomes derived from HNSCC cells had distinct effects on CAF gene expression towards pro-inflammatory or ECM modulating activities. This is reflected in enhanced neutrophil recruitment in the blood of HPV⁺ patients, and higher α SMA levels and collagen secretion in HPV⁻ tumors. Using this new understanding of TME may lead to exciting novel therapeutic approaches.

Results

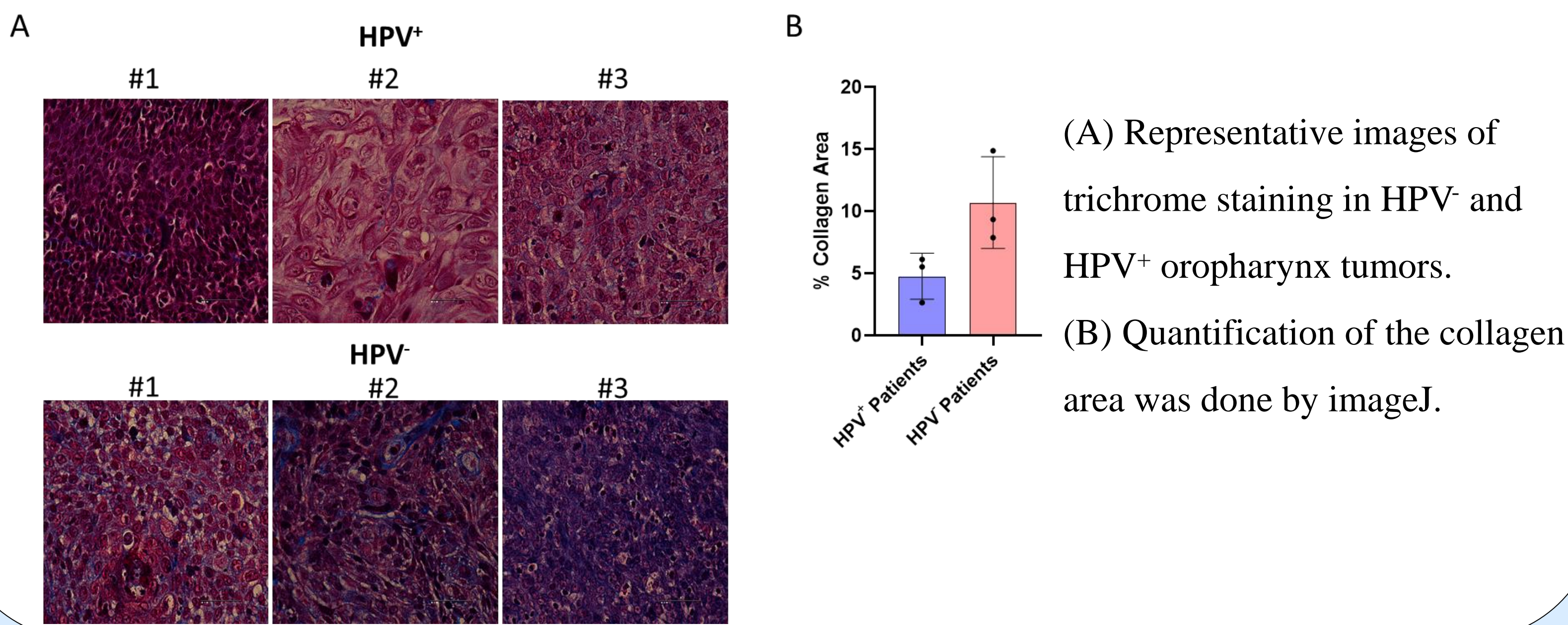
1. Exosome Isolation from Human HPV⁺ and HPV⁻ HNSCC Cell Lines



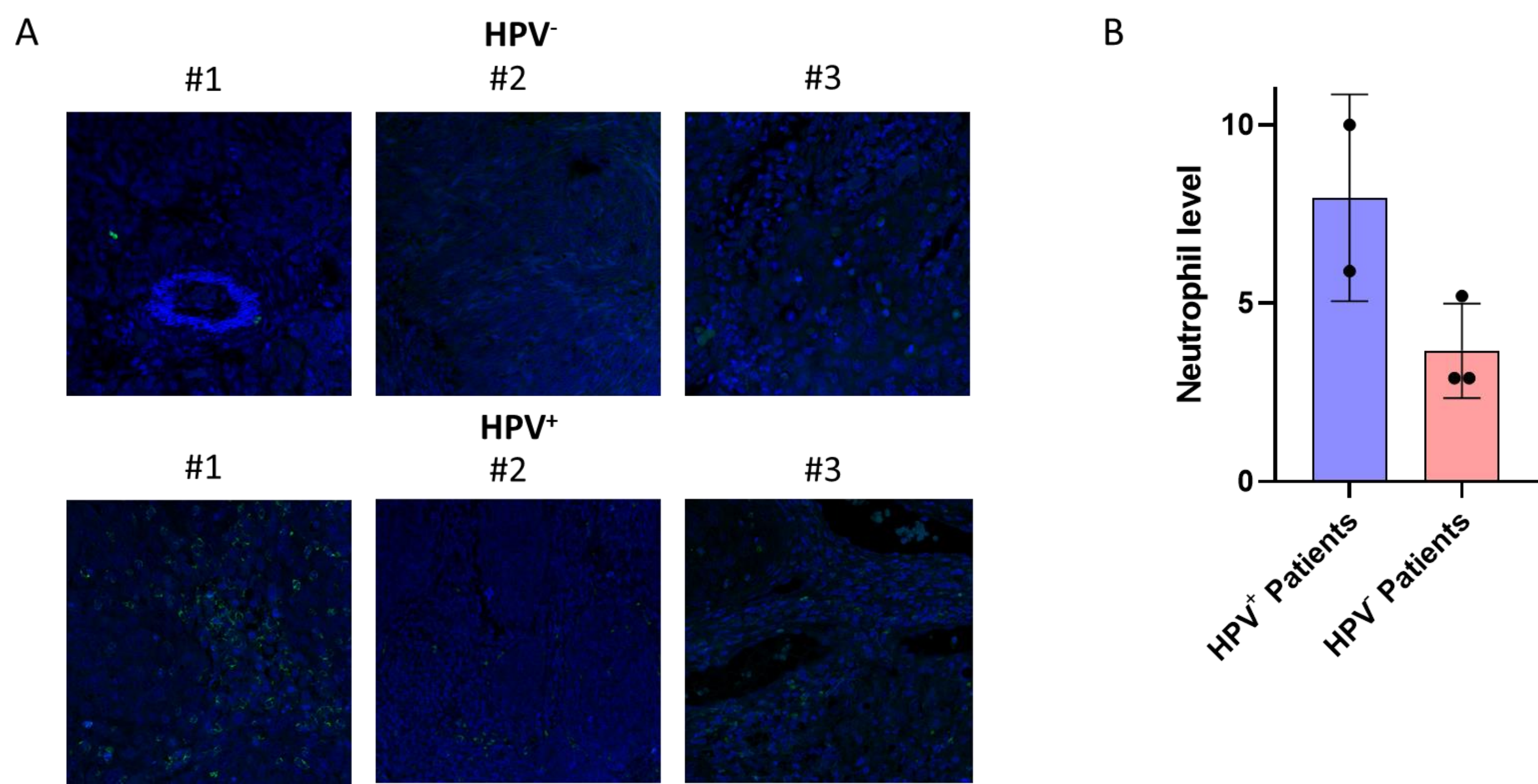
2. HPV⁺ Exosome-Derived miRs Downregulate TGF β R2 and α SMA mRNA Levels and Elevate CXCL1 and CXCL5 in Human Oral Fibroblasts



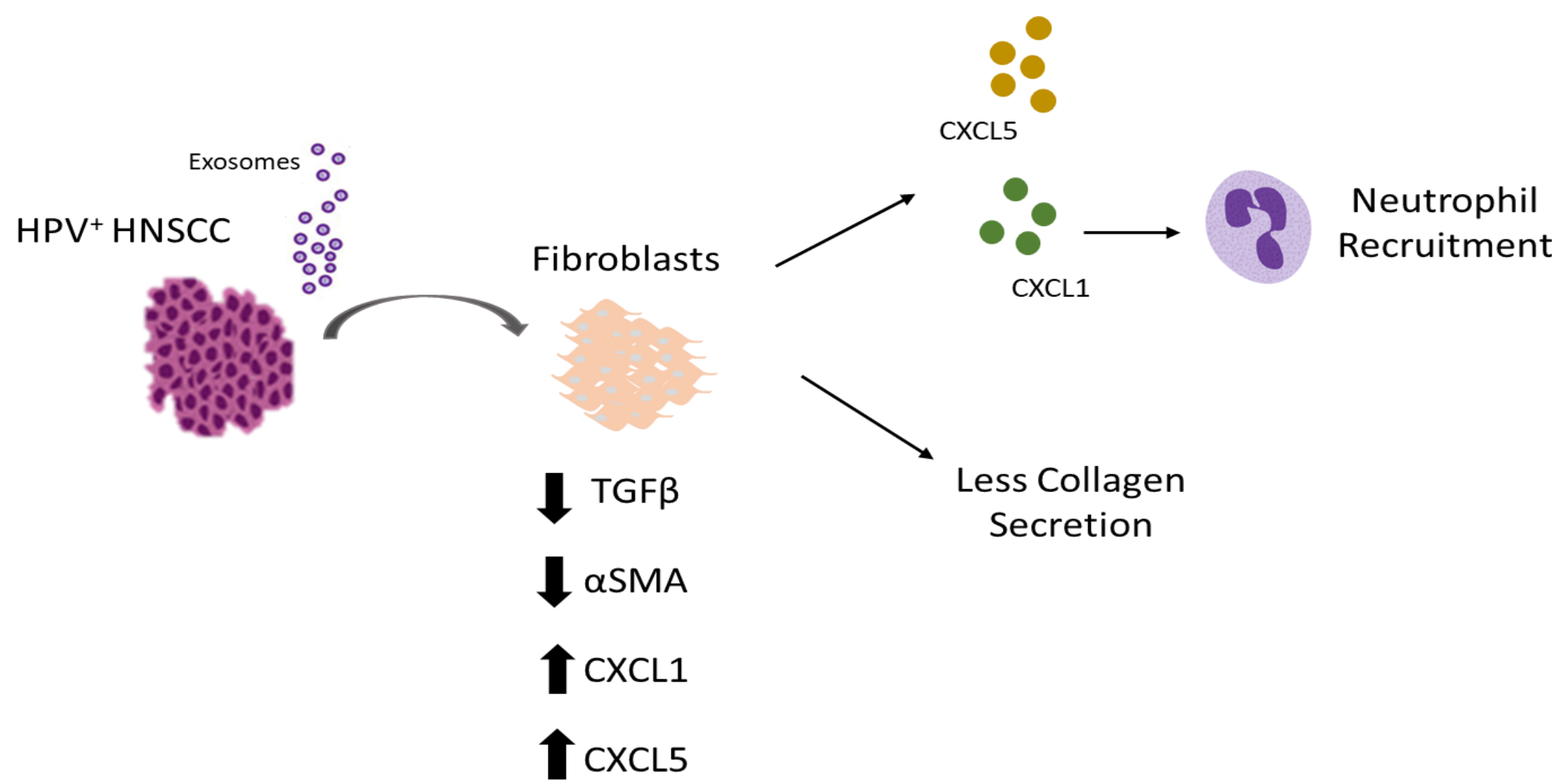
3. Higher Collagen Secretion in Human HPV⁻ Oropharynx Tumors



4. Higher Neutrophil Levels in HPV⁺ Oropharynx Tumors and Peripheral Blood



Suggested Model



Summary

- HPV⁺ HNSCC-derived exosomes contain miRs against targets in the TGF β pathway. .
- Fibroblasts in the TME of HPV⁺ tumors uptake the exosomes, which cause downregulation of TGFBR2, thus downregulation in α SMA and elevation in CXCL1 and CXCL5 gene expression.
- CXCL1 and CXCL5 act as neutrophil chemoattractants, thus higher levels of neutrophils in HPV⁺ vs HPV⁻ tumors.