Chemokine-mediated CDD8 T cell recruitment is an essential but not well-established event for the persistence of oral lichen planus (OLP). Semaphorin-4D (Sema4D) is a 150-kDa membrane-bound protein and it also exists as a 120-kDa soluble form (sSema4D) after shedding from cell surfaces with proteolytic. By interaction with several receptors, plexin-B1, plexin-B2 or CD17, Sema4D mediates effects on epithelial cells, endothelial cells and immune cells. Sema4D has been reported implicated in immune dysfunction, chemokine modulation and cell migration, which are critical aspects for OLP progression, but its implication in OLP pathogenesis has not been determined. In this study, we sought to explicate the effect of Sema4D on human oral keratinocytes and its capacity to drive CDD8 T cell lesonal trafficking via chemokine modulation. And also, the resource of sSema4D was investigated in our study.

INTRODUCTION

There is a amplified feedback loop involving MMP9, T cells, chemokines and Sema4D-dependent signaling that promotes CDD8 progression.

METHODS

Collection of peripheral blood, tissue transudates (TTs), and skin tissue from patients with OLP and healthy individuals; Primary human oral keratinocytes were cultured and treated with sSema4D; Enzyme-linked immunosorbent assay (ELISA) and Western blotting; Immunohistochemistry, Immunofluorescence and Western blotting Statistical analysis.

RESULTS

1. The expression of sSema4D was significantly reduced on OLP patients and the levels of sSema4D and MMP9 were parallelly increased in patient-derived serum and tissue transudates.

2. Incubation of healthy-derived PBMCs with pro-activated Sema4D caused a significant release of sSema4D into the culture supernatants.

3. sSema4D induces CXCL9 and CXCL10 expression in primary human oral keratinocytes.


5. Sema4D induces CXCL9 and CXCL10 expression in primary human oral keratinocytes.

6. Elevated CXCL9 and CXCL10 levels were positively correlated with sSema4D levels in OLP lesions and serum. The study was funded by the National Natural Science Foundation of China (no. 81430073, no. 81220108016, no. 81472863).

CONCLUSION

Our study showed that MMP-9 may cleaves Sema4D on infiltrated T cells, resulting in high levels of sSema4D in OLP lesions. By binding to plexin-B1 in oral keratinocytes, sSema4D activates the Akt-NF-κB cascade, inducing CXCL9 and CXCL10 production and secretion. CXCL9 and CXCL10 drives additional lesional trafficking of CDD8 T cells, hence creating an amplification feedback loop and maintaining the autoimmune response.

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