Semaphorin 3A Controls Allergic and Inflammatory Responses in Experimental Allergic Conjunctivitis

(セマフォリン 3A を用いたアレルギー性結膜炎に対する生物製剤治療法の開発)

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1. INTRODUCTION

Allergy has been called “the 21st century disease”. In Japan the prevalence of allergic conjunctival diseases is estimated to be as high as 15%–20% of the population and is on the rise (Takamura et al., 2011). Currently, therapies for ocular allergy have evolved to a point where there are now highly efficacious treatments for most of patients. Despite this, those with the most severe, chronic allergic conjunctivitis still experience substantial disease symptomatology. These patients represent up to 30% of all allergic conjunctivitis sufferers, and thus constitute a significant unmet need (Uchio, 2008).

Recent studies, the role of Semaphorin-3A (SEMA3A) in the immune system has been revealed partially. (i) Enhances DC (dendritic cells) migration into lymph nodes, (ii) Induces apoptosis in M-CSF (macrophage colony-stimulating factor)-derived macrophages, and (iii) Terminates the immune response (Lepelletier et al., 2007; Moretti et al., 2008; Ji et al., 2009; Schlahsa et al., 2014). SEMA3A is widely accepted by the concept of “immune semaphorin” (Kikutani and Kumanogoh, 2003). In this study, we investigated the therapeutic potential of SEMA3A in experimental allergic conjunctivitis (EAC) mice model.

2. MATERIALS AND METHODS

BALB/c mice were intraperitoneally sensitized (50μg on day 0, 5 and day 10) to short ragweed pollen (SRW) followed by repeated SRW eye drops challenges (2μg from day 11). Different concentrations of SEMA3A (10 U, 100 U, 1000 U) and PBS were adopted as a therapeutic agent or as control. Actively immunized mice were treated with the agent
just before or at the same time as the eye drop challenges. Ophthalmic group were challenged via eye drops with the dosage of 10μL per eye twice a day for 4 weeks. Mice were evaluated using Haematoxylin and eosin staining, Immunofluorescence and light microscope photographs. For comparison, five types of commercial ophthalmic formulations for allergy were quantified using clinical characteristics.

3. RESULTS

SEMA3A as a biological agent, showed the beneficial activity in ocular allergic processes and the less damage to the intraocular tissue. Clinical score of composite ocular symptoms of the mice treated with SEMA3A were significantly decreased both in the immediate phase and the late phase compared to those treated with commercial ophthalmic formulations and non-treatment mice. SEMA3A treatment attenuates infiltration of eosinophils into conjunctiva in EAC Mice. The score of eosinophil infiltration in the conjunctiva of SEMA3A1000U-treated group were significantly lower than low-concentration of SEMA3A treated groups and non-treated group. SEMA3A treatment also suppressed T-cell proliferation in vitro and decreased serum total IgE levels in EAC mice. Moreover, Treatment of Sema3A suppressed Th2-related cytokines (IL-5, IL-13 and IL-4) and pro-inflammatory cytokines (IFN-γ, IL-17 and TNF-α) release, but increased regulatory cytokine IL-10 concentration in the conjunctiva of EAC mice.

4. DISCUSSION

Eosinophils have been studied extensively in relation to priming, and are thought to be key players in the late phase and in chronic allergic conditions (Godthelp et al., 1996). This eosinophilic priming translates clinically to more severe allergic responses (Yuki et al., 2011). The suppression of eosinophil migration is a key in the treatment of allergic conjunctivitis.

Nrp-1, which was originally identified as a cell surface glycoprotein, functions as a SEMA3A receptor (Kolodkin et al., 1997). Nrp-1 has been identified as a specific marker for CD4+CD25+ regulatory T cells (Tregs) (Bruder et al., 2004). Recently, one report has suggested that Nrp-1 in Tregs contributes to prolonged contact between Tregs and DCs, which inhibits T cell activation at steady state (Sarris et al., 2008). Furthermore, Nrp-1+ Tregs preferentially produce IL-10 upon SEMA3A stimulation (Catalano, 2010). The secretion of SEMA3A by activated T cells during the immune response is delayed, suggesting that sema3A/Np-1 interactions participate in terminating the immune response, thus restraining overactivation. In fact, Regardless of the suppressive function that SEMA3A exerts in adaptive immune responses (Wen et al., 2010). As
described above and the findings in this study suggest that SEMA3A in Tregs exerts suppressive functions, presumably by mediating Treg stop signals on DCs and by producing regulatory cytokines.

Due to the insufficiency of the non-steroid eye drops, topical steroids are still being used in the treatment of serious allergic conjunctivitis cases because of their strong effects (Sherif and Pleyer, 2002). However, the long term continuous usage of the topical steroids results in corneal epithelial disorder refractory. Other side effects include increased intraocular pressure, secondary glaucoma and secondary cataract.

It’s clear that every allergic reaction in the eye, whether induced by natural or artificial challenge, not only evokes an allergic inflammatory response, but also changes the response to future exposures. The communication between mast cells, dendritic cells and T cells is intimate and constant, and thus our goal in developing treatments can be thought of as a balancing act: keeping the protective functions of the immune system intact while responding to the acute and chronic perturbations of ocular allergy.

In conclusion, to overcome the risks described above, for the first time our study demonstrated the therapeutic potential of SEMA3A for AC. SEMA3A as a biological agent, showed the beneficial activity in ocular allergic processes with less damage to the intraocular tissues. SEMA3A provides a new intervention strategy and potential therapy for ocular allergy; and could reduce or eliminate the usage of topical steroid. SEMA3A may be valuable presence as a therapeutic agent for allergic diseases.
REFERENCES


PUBLICATION LIST

I Main Thesis
Semaphorin 3A Controls Allergic and Inflammatory Responses in Experimental Allergic Conjunctivitis.
Junmi Tanaka, Hideo Tanaka, Nobuhisa Mizuki, Eiichi Nomura, Norihiko Ito, Naoko Nomura, Masayuki Yamane, Tomonobu Hida, Yoshio Goshima, Hiroshi Hatano, Hisashi Nakagawa.

II Sub-Thesis
Therapeutic potential of semaphorin 3A after corneal chemical injury.
Junmi Tanaka, Tomohiko Usui, Tetsuya Toyono, Seiichi Yokoo, Suguru Nakagawa, Satoru Yamagami, Shiro Amano.
Patent pending

III Reference Thesis
None