Göteborg, 2017

Dental acrylates and methacrylates

Interactions with the immune system

Akademisk avhandling

som för avläggande av odontologie doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Föreläsningssal 3, Odontologen, Medicinaregatan 12D, den 27 oktober, klockan 13:00.

av **Sara Alizadehgharib**

Fakultetsopponent:

Jon Einar Dahl, Professor

Universitetet i Oslo, Oslo, Norge

Avhandlingen baseras på följande delarbeten

I. **Alizadehgharib S**, Östberg AK, Larsson L and Dahlgren U. The immunomodulatory properties of 2-hydroxyethyl methacrylate are mediated by the NLRP3 inflammasome. Submitted for publication.

II. **Alizadehgharib S**, Östberg AK and Dahlgren U. Triethylene glycol dimethacrylate – adjuvant properties and effect on cytokine production. Submitted for publication.

III. Östberg AK, **Alizadehgharib S** and Dahlgren U. Sublingual administration of 2-hydroxyethyl methacrylate enhances antibody responses to co-administered ovalbumin and *Streptococcus mutans*. Submitted for publication.

IV. **Alizadehgharib S**, Östberg AK and Dahlgren U. Effects of the methacrylate/acrylate monomers HEMA, TEGDMA, DEGDA and EMA on the immune system. Submitted for publication.

V. Basic A, **Alizadehgharib S**, Dahlén G and Dahlgren U. Hydrogen sulfide exposure induces NLRP3 inflammasome-dependent IL-1β and IL-18 secretion in human mononuclear leukocytes *in vitro*. Clinical and Experimental Dental Research 2017 3:115-120.

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR ODONTOLOGI

GÖTEBORGS UNIVERSITET

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Abstract

Professionals working in dentistry have reported adverse effects, such as allergic contact dermatitis due to exposure to different methacrylates/acrylates. Leakage of such monomers from dental fillings due to incomplete curing is also common. Monomers are released into the oral cavity and some may also diffuse through the dentin and reach the dental pulp. In the tissue, monomers will come in contact with different cells of the immune system. At present, there is a lack of knowledge of the effects these monomers might have on cells. The main objective of this thesis was to investigate possible effects of four different methacrylate/acrylate monomers on the immune system *in vivo* and *in vitro*. The studied methacrylates and acrylate were ethyl methacrylate (EMA), diethylene glycol diacrylate (DEGDA), 2-hydroxyethyl methacrylate (HEMA) and triethylene glycol dimethacrylate (TEGDMA). In summary, our *in vivo* and *in vitro* results showed that:

- HEMA affects the immune system by inducing formation of the NLRP3 inflammasome (**Study I**).
- TEGDMA has adjuvant properties and the ability to modulate cytokine production from peripheral blood mononuclear cells, which may lead to interference with the normal immune response to various agents, self or non-self, present in the pulp and the oral mucosa (**Study II**).
- HEMA acts as a mucosal adjuvant when applied sublingually together with ovalbumin (OVA) or *Streptococcus mutans* in mice (**Study III**).
- The different monomers affect the production, increase as well as decrease, of various cytokines *in vitro* by peripheral blood mononuclear cells. Antibody production and T cell activity to OVA was increased in mice immunized with OVA in combination with methacrylates (**Study IV**).

Bacteria and bacterial products such as hydrogen sulfide (H_2S) challenge the oral mucosa. We wanted to investigate whether H_2S also affects the immune system in similar way as HEMA, i.e., induce formation of the NLRP3 inflammasome.

- Human mononuclear leukocytes exposed to H_2S had an enhanced production of NLRP3 inflammasome-dependent secretion of IL-1β and IL-18. (**Study V**). Thus, this may be a mode for H_2S to contribute to the inflammatory host response and pathogenesis of periodontal disease

In summary, the different methacrylate/acrylate monomers frequently used in dental restoration materials may interfere with the immune system in many different ways. The increase as well as the decrease in cytokine production from human mononuclear cells is affected by all these methacryleate/acrylate monomers. The T and B cell activity is also affected by all tested methacrylates . Thus, this may be a model that provide some insight into the nature of the immune responses to methacrylates and acrylates, and may advance the development of more biocompatible restorative materials in the future for clinical use.

Keywords: Methacrylates, acrylates, cytokines, immunoglobulin, B cell, T cell, macrophages, mouse, adjuvant

ISBN: 978-91-629-0244-5 (TRYCK) http://hdl.handle.net/2077/52846
ISBN: 978-91-629-0245-2 (PDF)