Understanding the regulatory requirements for Gut IgA B cell responses and their potential role in mucosal vaccine development

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i salen Arvid Carlsson på Göteborgs Universitet, torsdagen den 14 juni 2018, klockan 09:00

av Rathan Joy Komban

Fakultetsopponent:
Birgitta Heyman, Professor, PhD
Uppsala Universitet, Uppsala, Sweden

Avhandlingen baseras på följande delarbeten

I. Komban R., Strömberg A., Jakob Cervin., Cervin J., Yrlid U., Johannes Mayer, Simon Milling., Mats Bemark., and Nils Lycke. Orally activated B cells migrate via lymph to multiple Peyer's patches where they re-utilize germinal centres in an antigen and CD40-dependent fashion. Manuscript, 2018.

II. Komban R., Strömberg A., Biram A., Cervin J., Yrlid U., Shulman Z., Bemark M., and Lycke N. Activated Peyer's patch B cells sample antigen from M cells in the sub epithelial dome to maintain gut germinal center responses. Manuscript under revision in Nature Communications.

III. Bemark M, Hazanov H, Strömberg A, Komban R, Holmqvist J, Koster S, et al. Limited clonal relatedness between gut IgA plasma cells and memory B cells after oral immunization. Nat Commun 2016, 7: 12698.

IV. Komban R., Bergqvist B., Strömberg A., Bemark M., and Lycke N. Germ free mice exhibit poor gut IgA plasma cells responses but host intact and effective inductive sites in their Peyer´s patches. Manuscript.

INSTITUTIONEN FÖR BIOMEDICIN

ISBN: 978-91-7833-029-4 (TRYCK)
ISBN: 978-91-7833-030-0 (PDF)
http://hdl.handle.net/2077/55967

Understanding the regulatory requirements for Gut IgA B cell responses and their potential role in mucosal vaccine development

Rathan Joy Komban

Department of Microbiology and Immunology, Institute of Biomedicine, Sahlgrenska Academy at the University of Gothenburg, Sweden, 2018.

Abstract

It is important to understand gut B cell differentiation, from the activation of cells at inductive lymphoid sites to the formation of gut plasma and memory B cell, to be able to develop efficient oral vaccines but the process is incompletely defined. To address this we developed an adoptive transfer system based on B1-8^{hi}/GFP^{+} NP-specific B cells and NP-CT, a hapten-carrier complex that allows us to follow antigen-specific IgA responses following oral immunization. In paper (I) we provide evidence for early migration of activated B cells via draining lymph and blood to germinal centers (GC) in Peyer's patches (PP) spatially distinct from where the cells originated, thus explaining how synchronization between PP may be achieved. We address the requirements for activated PP B cells to re-enter GC, and demonstrate the necessity of antigen and expression of CD40 on B cells. Gut IgA plasma cells did not form from B cells lacking CD40 in a competitive bone marrow transfer experiment, suggesting that the GC pathway dominate their formation. In paper (II) we show that activated PP B cells interact with M cells and antigen in the sub epithelial dome (SED) of PP. B cells in SED had an IgD^{-}, $GL7^{-}$ and $CCR6^{+}$ phenotype and migrated rapidly towards the GC after interacting with antigen. We hypothesize that during a PP immune response, B cells intermittently sample and transport antigen from the basal pockets of SED M cells and that this feeds antigen into the GC to maintain the response. Paper (III) demonstrates that gut memory B cells and long-lived plasma cells are not closely clonally related. We propose that the plasticity of PP allows these two classes of B cells to evolve in temporarily or anatomically separate GC processes, leading to diverse low-affinity memory B cells and clonally restricted high-affinity plasma cells. In this way, the plasma cells are focused on antigens currently in the gut whereas a broader repertoire of memory cells is able to recognize related antigens. On reactivation, the mucosal memory B cell response was dominated by clonally selected, high-affinity cells, leading to the formation of plasma cells of high affinity. Paper (IV) demonstrates that germ free (GF) mice largely lack IgA producing plasma cells despite having intact B cell expansion and differentiation in PP GC. This suggests that lack of bacterial colonization is associated with that the gut lamina propria (LP) cannot attract and/or host IgA producing plasma cells. An oral immunization with NP-CT did not only induce antigen-specific IgA plasma cells in the LP but also largely restored polyclonal IgA production in the gut. Thus, in GF mice, CT induced the LP effector site to attract polyclonal IgA producing plasma cells in a manner similar to that seen following bacterial colonization. Taken together, this thesis demonstrate several features that are unique to activated gut B cells, and show that these are relatively mobile and not as restricted to a single GC as during systemic responses.

Keywords: [Germinal centers, Sub-epithelial dome, NP-CT, B1-8hi/GFP+ NP-specific B cells, Peyers patches, Lamina propria, Germ free mice]

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