ERF8

Programme Jeunes chercheuses, jeunes chercheurs 2007

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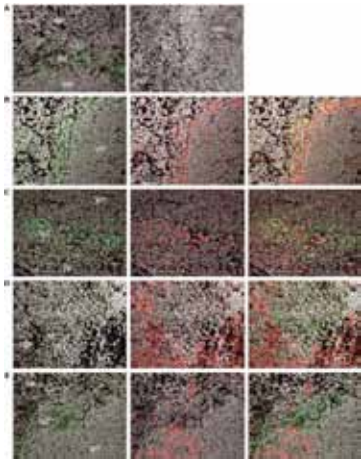
Antigen presenting cells in alloimmune response to factor VIII (FVIII): exploring innovative therapeutics through the molecular dissection of endocytic pathways

Context

Hemophilia A is a rare X chromosome-linked recessive disease. In its severe form, hemophilia A is a life-threatening, crippling hemorrhagic disease. Treatment of hemophilia patients with therapeutic FVIII results, in up to 30% of the cases, in the mounting of anti-FVIII immune responses and in the emergence of anti-FVIII antibodies (inhibitors) that neutralize the procoagulant activity of the therapeutically administered FVIII.

Objectives

- ✧ To understand the process of immune response to FVIII
- ✧ To study the implication of antigen presenting cells and their endocytic receptors in the uptake of FVIII
- ✧ To design therapeutic tools to prevent the anti-FVIII immune response



In situ localization of FVIII in the spleen of FVIII-deficient mice. *FVIII-deficient mice were injected with FVIII or PBS, and sacrificed 30 min later. (**A**). FVIII (green) was detected on histological spleen sections in the case of FVIII- (left panel) and PBS-treated mice (right panel). (**B, C, D,E**) Histological sections of spleens of FVIII-treated mice were labeled with anti-FVIII antibodies (Green), and with MOMA-1, anti-MARCO, anti-F4/80 or anti-CD11c (B, C, D and E, respectively) antibodies (Red). Left panels show FVIII staining alone, middle panels show MOMA-1, MARCO, F4/80 or CD11c staining alone and right panels show merged images. Data are representative of 3–4 mice in each group. MZ, marginal zone, WP, white pulp, RP, red pulp, as identified using MOMA-1 and anti-F4/80 antibodies. Magnification 40X.*

Results

- ❖ CD91 and other members of the low-density lipoprotein receptor family are not strongly implicated in FVIII uptake by human dendritic cells (DC), the professional antigen presenting cells (APC) that participate in the initiation of the primary anti-FVIII immune response, i.e in previously untreated naïve hemophilia A patients.
- ❖ Using FVIII-deficient mice as a model for hemophilia A, we found that FVIII preferentially accumulates in the spleen at the level of metallophilic macrophages in the marginal zone (MZ). Surgical removal of the spleen or selective *in vivo* depletion of macrophages and CD11c-positive CD8α-negative DC resulted in a drastic reduction in anti-FVIII immune responses.
- ❖ CD4+CD25+ regulatory T cells modulate functions of antigen presenting cells
- ❖ Plasma-derived FVIII induces lower levels of inhibitors than recombinant FVIII, and that Von Willebrand factor (VWF) is an immuno-chaperone molecule for FVIII
- ❖ CD206 is identified as a new catabolic receptor for FVIII
- ❖ Induction of heme oxygenase-1, a stress-inducible enzyme with potent anti-inflammatory activity, in FVIII-deficient mice reduces the immune response to therapeutic FVIII
- ❖ Bortezomib (a proteasome inhibitor which depletes plasmocytes) delays the onset of FVIII inhibitors in experimental hemophilia A, but fails to eliminate established anti-factor VIII IgG-producing cells

Conclusions-Perspectives-Impact

This ANR project provided data on (i) endocytic receptors implicated in uptake of FVIII by DC (ii) the nature of the secondary lymphoid organs and relative contribution of various APC in the initiation of immune responses to FVIII (iiii) role of CD206 on catabolism of FVIII *in vivo* (iv) exploitation of HO-1 pathway for reducing anti-FVIII inhibitor development following repeated infusion of FVIII and (v) therapeutic utility of proteasome inhibitor to prevent the development of and to eradicate FVIII inhibitors.

In the future, we aim to confirm whether CD206 plays a role in the clearance of therapeutic FVIII in patients, and whether altering FVIII-CD206 interaction in patients prolong the half-life of the therapeutic molecule.

Altogether, results from this project carry an enormous potential for reducing the cost related to treatment of patients and to initiate clinical trials on the novel therapeutic strategies for hemophilia A patients based on either cellular or drug-mediated therapy.

Publications-Valorisation

- ➢ Dasgupta et al., *Haematologica* 93:83-89 (2008)
- ➢ Lacroix-Desmazes et al., *Blood* 112:240-249 (2008)
- ➢ Dasgupta et al., *J Immunol.* 181:1609-1615 (2008)
- ➢ Bayry *Nat Rev Rheumatol.* 5:244-245 (2009)
- ➢ André et al., *Am J Pathol.* 174:1575-1887 (2009)
- ➢ Navarrete et al., *J Thromb Haemost.* 7:1816-1823 (2009)
- ➢ Navarrete et al., *Arthritis Rheum.* 60:2848-2849 (2009)
- ➢ Dimitrov et al., *Mol Immunol.* 47:290-297 (2009)
- ➢ Dimitrv et al., *Blood* 115:2682-2685 (2010)
- ➢ Navarrete et al., *Thromb Haemost.* 104:1093-1098 (2010)
- ➢ Meslier et al.,. *J Thromb Haemost.* 9:719-728 (2011)

◆ Lacroix-Desmazes S, Dasgupta S, Bayry J and Kaveri SV. "Demannosylated recombinant factor VIII for the treatment of patients with hemophilia A". INSERM – Laboratoire Français du Fractionnement et des Biotechnologies. 2008 (WO/2008/129422) http://www.wipo.int/pctdb/en/wo.jsp?WO=2008129422

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