Immunosuppressive role of fibrinogen-like protein 2 (FGL2) in CD8+regulatory T cells-mediated long-term graft survival

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Immunosuppressive role of fibrinogen-like protein 2 (FGL2) in CD8$^+$regulatory T cells-mediated long-term graft survival

Séverine Bézie[1*], Séverine Ménoret[2], Laurent Tesson[2], Xian-Liang Li[1], Claire Usal[1], Ignacio Anegon[1], Lise Caron[1]

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Background

We have previously reported that, in a model of cardiac allograft in rat, blockade of CD40-CD40L interaction induces long-term graft survival mediated by CD8$^+$ CD45RC^{low} regulatory T cells (Tregs) [1]. Transcriptomic comparison of Tregs from AdCD40Ig-treated vs naïve rats highlighted the overexpression of FGL2 whose immunoregulatory properties are little known [2].

Material and methods

A lewis 1W rat heart is grafted in a MHC-mismatched Lewis 1A rat and infected with 2.10^{10}pi of adenovirus recombinant for CD40Ig molecule (AdCD40Ig) the day of the graft. Tregs, effector CD4$^+$CD25$^-$ T lymphocytes (TL), and plasmacytoïde dendritic cells (pDC) from spleen are sorted by FACS Aria for *in vitro* tests. For *in vivo* studies, 4,5.10^{11}vg of FGL2-recombinant adenovirus associated virus (AAVFGL2) are intramuscularly or intravenously injected in recipients 30 days before the graft. Splenocytes are transferred to sublethaly irradiated rats by *i.v* injection the day before the graft.

Results

We confirmed FGL2-overexpression in splenic Tregs and in the graft of AdCD40Ig-treated vs non-treated and naïve rats, at mRNA and protein level. FGL2 involvement in Tregs immunosuppressive function was proved by *in vitro* and *in vivo* experiments. Indeed, Tregs from AdCD40Ig-treated rats inhibit TL proliferation in response to allogeneic pDC. This inhibition is abrogated by FGL2-blocking antibodies [3] and can be mimicked by FGL2 protein alone. Moreover, AAV-mediated FGL2 overexpression in rat prolongs graft survival with a median of 18.5 days vs 11 days for controls by i.m injection and survival is improved when i.v injected. Furthermore, adoptive transfer of splenocytes from an AAVFGL2-treated tolerant rat, to irradiated rats, transmits long-term graft survival iteratively.

Conclusions

This is the first demonstration that the immunosuppressive molecule FGL2 is able to induce a long-term graft survival and that this tolerance is active and transferable by splenocytes. Work is under progress to identify the population responsible for this infectious tolerance.

Author details
[1]INSERM UMR 643, Nantes, France. [2]Plateform Transgenic Rats Nantes IBiSA-CNRS, Nantes, France.

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[1]INSERM UMR 643, Nantes, France
Full list of author information is available at the end of the article