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ORAL PRESENTATION

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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 Ménoret², Laurent Tesson², Xian-Liang Li¹, Claire Usal¹, Ignacio Anegón¹, Lise Caron¹

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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 2.10¹⁰ 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, 4,5.10¹¹vg of FGL2-recombinant adenovirus associated virus (AAVFGL2) are intramuscularly or intravenously injected in recipients 30 days before the graft. Splenocytes are transferred to sublethally 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

¹INSERM UMR 643, Nantes, France. ²Plateform Transgenic Rats Nantes IBIISA-CNRS, Nantes, France.

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¹INSERM UMR 643, Nantes, France

Full list of author information is available at the end of the article