Long-term graft tolerance induction by NFATc pathway inhibition in innate immune cells

Gornati L.[1]*, Cigni C.[1], Mingozzi F.[1], Marongiu L.[1], Rotem R.[1], Colombo M.[1], Prosperi D.[1], Zanoni I.[1,2], Granucci F.[1]

*l.gornati@campus.unimib.it
[1] University of Milano – Bicocca, Department of Biotechnology and Biosciences, piazza della Scienza 2, 20126, Milan, Italy
[2] Harvard Medical School, Boston Children's Hospital, Boston, MA, USA.

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The Nuclear Factor of Activated T cells (NFAT) is a transcription factor that has been always associated to T cell elicitation since its activation via calcium and calcineurin (Cn) results in the expansion of lymphocytic clones via NFAT-dependent interleukin (IL)-2 production. Recently, NFAT has emerged as a fundamental factor also in innate immunity, as in dendritic cells (DCs), being activated downstream pathogen recognition receptors (PRRs) engagement. Furthermore, IL-2 production and trans-presentation by DCs to naïve T cells represents a crucial event for their elicitation. Therefore, the aim of our study is to evaluate the role of NFAT in innate immunity in the context of mismatched transplantation, in which overt adaptive response occurs via DCs-mediated antigen presentation. By taking advantage of a minor antigen-based mismatched transplant setting, we grafted NFATc2 KO male-derived skin into C57BL/6 WT female recipients and monitored acute rejection. Compared to the WT counterpart, recipients of NFATc2 KO male skin exhibited delayed rejection, since NFATc2 activation in donor cells occurs rapidly after transplantation and promote rejection. The absence of NFATc2 in the skin graft revealed to be sufficient to reduce the IFN-γ production in the skin by recipient's infiltrating immune cells and to limit donor DCs maturation and migration to the graft-draining lymph nodes (LN), thus affecting DCs antigen presentation to naïve alloreactive T cells in the LN. To deepen the role of the NFAT members in innate immunity, our collaborators of the NanoBioLab provided us with a novel nano-tool to selectively target phagocytes, hence also DCs, with an NFAT specific inhibitor: the VIVIT peptide. Indeed, the conjugation of VIVIT to nanoparticles (NPs) allowed us to exploit the intrinsic capability of phagocytes to engulf external particulates. By treating the animals with VIVIT NPs, even for a limited time window after transplantation, we obtained the complete acceptance of the graft thanks to the expansion of skin graft-specific CD4+ CD25+ Foxp3+ regulatory T cells (Tregs). Therefore, not only VIVIT-NPs constitute a novel approach to study the role of NFAT in innate immunity, but they may also represent an efficacious therapeutic strategy for grafted patients that are currently long-life administered with Cn inhibitors, subjected to severe side effects.