Dimerization partner shift of MafB determines macrophage polarization

---
Macrophages are plastic cells that adapt their activation states depending on their microenvironment. However, how macrophages integrate the microenvironment into their transcriptional machineries that determine these activation states is still not well defined.

Here we show that in macrophages, the expression of alternative dimerization complexes of the bZIP transcription factor (TF) MafB with itself or with c-Fos induces either ant-inflammatory or pro-inflammatory functions, respectively.

bZIP TFs have the ability to homo-dimerize or to form hetero-dimers with other bZIP factors. But distinct functions of such complexes have been difficult to identify. Here we address this problem by selectively re-introducing the expression of either MafB/MafB or MafB/c-Fos complexes in MafB/c-Maf deficient macrophages. Using this approach and ChIP-Seq experiments we show that these alternative complexes bind different consensus DNA motifs, have a distinct genomic binding repertoire selecting different enhancer and promoter regions and consequently drive differential gene expressions. These gene expression profiles of MafB/c-Fos or MafB/MafB expressing macrophages are enriched for pro-inflammatory (M1-like) or immuno-suppressive (M2-like) macrophage polarization signatures. Consistent with this, M1- or M2-like polarization of WT bone marrow-derived macrophages (BMMs) with LPS/IFNγ or Il-4 induces MafB/c-Fos or MafB/MafB complexes and MafB/c-Fos or MafB/MafB regulated gene expression, respectively.

Functionally, MafB/MafB or MafB/Fos expressing macrophages show opposite repressive or stimulatory effects in the regulation of syngeneic and allogeneic T cell activation in vitro, compared to Maf-deficient macrophages. In vivo, injections of macrophages expressing MafB/MafB complexes have a beneficial impact on mice survival after high-dose LPS septic shock. By contrast, injections of macrophages expressing MafB/c-Fos show exacerbated inflammation induced by low-dose LPS. Moreover, in our newly generated mouse model selectively favouring MafB/c-Fos dimerization we observe increased death rate, morbidity and inflammatory cytokine expression after LPS-induced septic shock.

Our novel approach using reconstitution experiments demonstrates that the same TF can engage in opposite macrophage polarization read-outs by being re-commissioned by an environment induced dimerization partner into a new DNA target and gene expression profile. This has wider implications for macrophage interactions with their environment and potential novel therapeutically applications exploiting Maf TF dimerization potential.

Keywords : MafB, c-Fos, transcription factor dimerization, macrophage polarization, macrophage activation
Authors :
References : , , ,

Authors

Hao Huang 1, Laurent Vanhille 2, Julien Maurizio 2, Jérémy Favret 3, Wilfried Cathou 2, Caroline Huber 2, Hassiba Belahbib 2, Ziming Weng 4, Pierre Perrin 2, Thien Phong Vu Mahn 2, Carole Berruyer 2, Michael Sieweke 5,

1. Center for Regenerative Therapies TU Dresden (CRTD); Aix Marseille Univ, CNRS, INSERM, Centre d'Immunologie de Marseille-Luminy, Dresden, GERMANY
2. Aix Marseille Univ, CNRS, INSERM, Centre d'Immunologie de Marseille-Luminy, Marseille, FRANCE
3. Center for Regenerative Therapies TU Dresden (CRTD), Dresden, GERMANY
4. Department of Pathology, Stanford University, Stanford, UNITED STATES
5. Center for Regenerative Therapies TU Dresden (CRTD); Aix Marseille Univ, CNRS, INSERM, Centre d'Immunologie de Marseille-Luminy; Max-Delbrück-Centrum für Molekulare Medizin in der Helmholtzgemeinschaft (MDC), Dresden, GERMANY