Resolving the Kupffer cell niche

Macrophages form a heterogeneous group of immune cells which contribute to tissue-homeostasis by performing functions fitting with the requirements of their specific tissue of residence. These tissue-specific functions are acquired through induction of transcription factors (TFs) which control the expression of a number of tissue-specific genes. Expression of these TFs is regulated by a combination of tissue-specific signals produced by the local environment of the macrophage or “macrophage niche”.

By using a Kupffer cell (KC)-specific depletion model we first aim to identify the different cell types constituting the KC niche by analyzing the cells in contact with the resting KC or the monocytes developping in KC as well as their role in monocytes engraftment in the liver following KC depletion. We then highlight the molecules involved in niche cell activation and aim to unravel the signals produced by the KC niche and the TFs they induce which drive KC development. To do so, we combined multi-parameter flow cytometry, RNA-seq, KC-specific mouse models, prediction algorithms and in vitro systems. Comparative genetic analysis of the developing KC and other tissue-resident macrophages revealed a set of TF mostly, if not only, expressed by KC, including LXRα and SpiC that are upregulated during the initial stages of KC development. Coculture of bone-marrow monocytes with the different niche cell candidates showed that these two TFs were exclusively upregulated when cocultured with Liver Sinusoidal Endothelial Cells (LSECs) We then used a novel prediction algorithm named NicheNet to understand which signal expressed by the LSECs induced SpiC and LXRa.The top predicted interaction was found between DLL4 produced by LSECs and NOTCH1/2 expressed by liver-infiltrating monocytes. To validate this prediction, we cocultured monocytes and DLL4-expressing cells. This induced expression of LXRα, SpiC and KC-identity genes. Furthermore, in vivo blocking of DLL4 drastically reduces SpiC expression on developing monocytes and as a significant effect on LXRa expression. Thus, we have shown that DLL4 expressed by LSECs is a tissue-derived signal inducing the expression of LXRα, SpiC and KC-identity genes during KC development.

Keywords : Macrophage, Kupffer cell, niche, development, transcription factors
Authors :
References : , , ,

Authors

Johnny BONNARDEL 1,

1. Inflammation research center, VIB, Gent, BELGIUM