Inflammation is a hallmark of many common diseases ranging from arthritis, atherosclerosis, or obesity to Alzheimer's disease and cancer. Identifying anti-inflammatory mechanisms is therefore an important and timely task of modern medicine. In this issue of *The EMBO Journal*, a study conducted by Escolano and colleagues target a particular interaction site of calcineurin with NFAT in macrophages to elicit profound anti-inflammatory effects (Escolano et al., 2014).

See also: A Escolano et al (May 2014)

The findings presented by Escolano et al open up new avenues targeting macrophages to repress the inflammatory responses seen in many common diseases. However, before this approach can be applied to patients, important questions need to be answered: For example, what is the relationship of anti-inflammatory macrophages induced by the LxVP peptide with other anti-inflammatory macrophages? Global transcriptome or proteome analyses would allow addressing this question in a comprehensive fashion (Xue et al., 2014). Such data might also be used to determine major downstream effector mechanisms that execute calcineurin blockade by the LxVP peptide. Since there seem to be significant differences between the LxVP peptide and other inhibitors of calcineurin, global assessment of changes in gene expression in response to these different...
inhibitors might quickly lead to an understanding of the profound differences in anti-inflammatory properties in macrophages. This area of research needs further exploration, particularly since previous work with CsA and FK506 (Kang et al, 2007) did similarly not reveal the molecular basis of this intriguing phenomenon.

Moreover, such genome-wide data might be utilized to identify specific markers of these cells that could serve as biomarkers to monitor the efficacy of LxVP peptide-based therapeutic approaches in vivo. Another issue concerns the translation of these findings to a clinical setting. Escolano et al suggest cell therapy with CN-gene-deleted or LxVP-inhibited macrophages or alternatively the use of lentiviruses for delivery of the LxVP peptide-encoding RNA. However, a specific blockade of calcineurin in macrophages directly in vivo by a chemical compound might be a much more appealing approach, particularly to be picked up by biotech or the pharmaceutical industry. The seemingly higher specificity of the LxVP peptide among the CNIs and the novel approach to directly target macrophages warrant further investigation into its possible benefits in the context of a variety of diseases that are known to present with macrophage-associated or macrophage-mediated inflammation.

Conflict of interest
The author declares that he has no conflict of interest.

References

Figure 1. In macrophages, the LxVP peptide can inhibit the interaction of calcineurin (CN A and CN B) with NFAT. This blockade leads to reduced activity of MKP-1, a dual specificity protein phosphatase. Reduced activity of MKP1 itself results in increased activity of p38 MAPK, which is associated with reprogramming of macrophages to become anti-inflammatory. In murine in vivo models, these anti-inflammatory macrophages inhibit the inflammatory model diseases: collagen-induced arthritis, zymosan-induced acute paw inflammation and oxazolone-induced contact hypersensitivity.