Nature Reviews Immunology | AOP, published online 10 July 2015; doi:10.1038/nri3886

T CELL DIFFERENTIATION

NLRP3 goes beyond the inflammasome

NLRP3 (NOD-, LRR- and pyrin domain-containing 3) is an important inflammasome component, but it is unclear whether it has any other immune functions. Now, Bruchard *et al.* show that NLRP3, independently of inflammasome activation, regulates the differentiation of T helper 2 (T_H2) cells and has a role in asthma and T_H2 cell-dependent tumour growth.

To investigate the role of NLRP3 in $CD4^+$ T cell differentiation, the authors examined *Nlrp3* mRNA expression in naive mouse $CD4^+$ T cells, in T cell receptor (TCR)-activated mouse $CD4^+$ T cells cultured in the absence of differentiating cytokines (T_H0) and in $CD4^+$ T cells polarized into T_H1 cells or T_H2 cells. *Nlrp3* mRNA expression was increased in T_H0, T_H1 and T_H2 cells at 12 hours after activation but not in naive mouse $CD4^+$ T cells. However, *Nlrp3* deficiency only had an effect on T_H2 cell polarization; expression levels of the T_H2 cell-specific cytokine interleukin-4 (IL-4) were decreased in *Nlrp3*$^{-/-}$ T_H2 cells, whereas expression levels of the T_H1 cell-defining cytokine interferon-γ in *Nlrp3*$^{-/-}$ T_H1 cells were similar to wild-type cells. Thus, NLRP3 is expressed during the differentiation of $CD4^+$ T cells and is specifically involved in the polarization of T_H2 cells.

T_H0, T_H1 and T_H2 cells expressed similar levels of NLRP3, suggesting a common stimulus for *Nlrp3* induction. Stimulation of the TCR, which drives IL-2 secretion, is required for the differentiation of these $CD4^+$ T cell subsets and could therefore have a role in the control of *Nlrp3* expression. Indeed, inhibition of IL-2 abolished the ability of TCR triggering to induce the expression of *Nlrp3* mRNA in $CD4^+$ T cells. In addition, stimulation of $CD4^+$ T cells with IL-2 in the absence of TCR triggering increased *Nlrp3* mRNA expression. Hence, IL-2 signalling induced NLRP3 expression.

NLRP3 is normally located in the cytoplasm of macrophages, where it forms an inflammasome complex with the adaptor protein ASC and caspase 1. However, in T_H2 cells NLRP3 was located in the nucleus and was unable to induce inflammasome activation. Instead, NLRP3 bound directly to DNA in the promoter regions of T_H2 cell-related genes. Further analysis showed that NLRP3 interacts with interferon-regulatory factor 4 (IRF4) — which is a transcription factor controlling the T_H2 cell programme — at the *Il4* promoter, and this interaction was required for optimal IRF4-dependent *Il4* transcription.

Finally, the authors tested the *in vivo* relevance of their observations. In a mouse model of ovalbumin (OVA)-induced allergic asthma — which is driven by T_H2 cell responses — OVA-treated *Nlrp3*$^{-/-}$ mice had less infiltration of eosinophils and lymphocytes into the lungs and lower levels of T_H2 cell-related cytokines than wild-type, ASC-deficient or caspase 1-deficient mice. Furthermore, in a melanoma model in which lung metastasis are generated, tumour growth was shown to induce the expression of T_H2 cell cytokines in wild-type mice, whereas *Nlrp3*$^{-/-}$ mice with the same tumours produced decreased levels of IL-4. T_H2 cell polarization and IL-4 have been linked with the promotion of tumour growth in some animal models and, interestingly, the authors found that the growth of lung tumours was limited in *Nlrp3*$^{-/-}$ mice compared with wild-type mice.

In conclusion, this study shows that NLRP3 is not only a key inflammasome component but also a transcription factor that controls T_H2 cell polarization, and this has implications in asthma and cancer.

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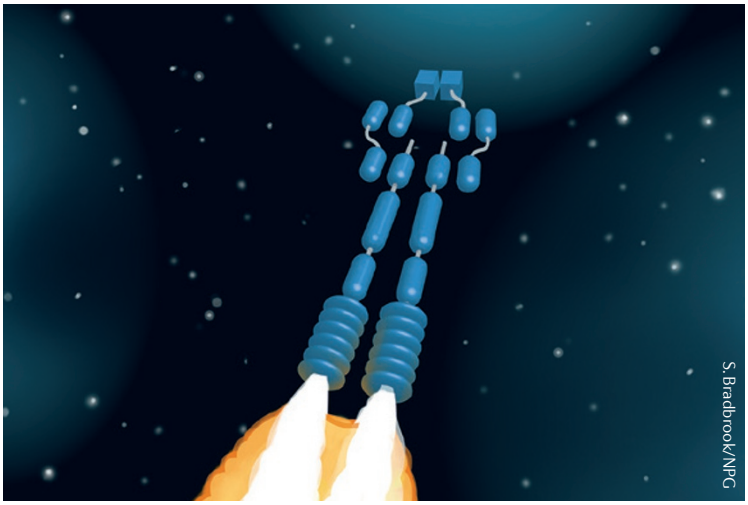
ORIGINAL RESEARCH PAPER Bruchard, M. *et al.* The receptor NLRP3 is a transcriptional regulator of T_H2 differentiation. *Nat. Immunol.* http://dx.doi.org/10.1038/ni.3202 (2015)



> NLRP3 bound directly to DNA