Nature Reviews Immunology | Published online 14 Nov 2016; doi:10.1038/nri.2016.126

Journal club

A THIRD SIGNAL FROM CONDITIONED DCS DICTATES MICROBIAL EFFECTOR CHOICE

There are special moments in our lives as scientists when we come across a conceptual synthesis that sheds enormous light on our own research. I enjoyed such an illuminating experience when I discovered the elegant papers of Martien Kapsenberg and Pawel Kalinski on the role of dendritic cells (DCs) in immune polarization. Their work, in common with my own, addressed a core question in microbial immunity regarding how different infectious agents (such as bacteria, protozoa, worms and viruses) trigger distinct $CD4^+$ T helper (T_H) cell responses.

The prevailing view of T_H cell differentiation at the start of the 21st century was that T_H1 versus T_H2 cell fate was determined by quantitatively and qualitatively distinct signals relating to T cell receptor (TCR) signal strength, co-stimulation or the cytokine milieu. However, the cellular source of these signals and how infectious agents might trigger them were poorly understood. Kapsenberg and Kalinski proposed a three-signal model of immune polarization in which these functions were all determined by one cell, the DC, through its distinct innate responses to different microorganisms. In their model, T_H cell differentiation requires a third signal delivered by the DC, in addition to MHC–peptide–TCR ligation ('signal 1') and costimulatory molecule engagement ('signal 2'). Signal 3 was loosely defined and included other stimuli (such as prostaglandins), in addition to polarizing cytokines. Importantly, Kapsenberg and Kalinski introduced the concept of DC 'conditioning', whereby exposure to specific microbial products determines the differentiation of DCs to provide a specific type of signal 3. They provided evidence to support this principle using an *in vitro* model of human $CD4^+$ T cell differentiation (*J. Immunol.*, 2002).

> "exposure to specific microbial products determines the differentiation of DCs to provide a specific type of signal 3"

The concept of DC conditioning as a crucial determinant of T cell fate has recently been called into question by data suggesting a more important role for pre-existing DC subsets that are 'hard-wired' to provide different types of signal 3. Although the evidence for this concept is compelling, we should not ignore the general plasticity of DCs and their ability to differentiate in distinct directions in response to specific pathogens. This is the concept so clearly formulated by Kapsenberg and Kalinski and supported by many of us who followed in their footsteps.

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The author declares no competing interests.

ORIGINAL ARTICLE de Jong, E. C. *et al.* Microbial compounds selectively induce Th1 cell-promoting or Th2 cell-promoting dendritic cells *in vitro* with diverse Th cell-polarizing signals. *J. Immunol.* **168,** 1704–1709 (2002)

FURTHER READING Kalinski, P. *et al.* T-cell priming by type-1 and type-2 polarized dendritic cells: the concept of a third signal. *Immunol. Today* **20**, 561–567 (1999) | Kapsenberg, M. L. Dendritic-cell control of pathogen-driven T-cell polarization. *Nat. Rev. Immunol.* **3**, 984 – 993 (2003)