AUTOIMMUNITY

Keeping CD4+ T cells under control

CD4+ T cells in the periphery are tightly controlled because inappropriate cell division, differentiation into effector cells or cell survival could lead to autoimmunity. A recent study, published in *The Journal of Experimental Medicine*, now shows that GADD45β (growth arrest and DNA-damage-inducible 45β) and GADD45γ provide one mechanism to keep peripheral CD4+ T cells under control.

GADD45β and GADD45γ have previously been shown to be crucial for the initiation of T helper 1 (T_H1)-cell immune responses and this has been attributed to their effect on p38-mitogen-activated protein kinase. However, in other cell types, they have a role in regulating cell-cycle progression and cell death; so, Liu *et al.* set out to investigate the role of GADD45β in regulating T-cell proliferation. Following stimulation through the T-cell receptor, GADD45β-deficient T cells underwent more rounds of cell division than GADD45β-sufficient control T cells. Similarly, when stimulated with interleukin-12 (IL-12) and IL-18, GADD45β-deficient T_H1 cells divided more times than control cells. In addition, GADD45β-deficient T_H1 cells showed increased resistance to activation-induced cell death (AICD).

Consistent with a role for GADD45β in controlling T-cell proliferation and susceptibility to AICD, GADD45β-deficient mice were more susceptible than control mice to experimental autoimmune encephalomyelitis (EAE). This increase in disease was caused by a T-cell defect because recombination-activating gene 1 (RAG1)-deficient recipients of GADD45β-deficient CD4+ T cells were also more susceptible to disease than recipients of wild-type control cells; and it was associated with T_H1-cell infiltration of the central nervous system.

Consistent with a synergistic role for GADD45β and GADD45γ in regulating T-cell proliferation and susceptibility to AICD, mice lacking both GADD45β and GADD45γ had

IMMUNE RESPONSES

Inhibition zipped

In a recent report in *Blood*, Cohen *et al.* indicate that the transcription factor glucocorticoid-induced leucine zipper (GILZ) has a crucial role in determining whether dendritic cells (DCs) stimulate or tolerize T cells. Moreover, it provides a common mechanism for the inhibition of DC maturation by interleukin-10 (IL-10) and glucocorticoids.

Optimal activation of T cells requires interaction between the co-stimulatory molecules CD80 and CD86 (expressed by DCs) and CD28 (expressed by T cells). By contrast, anergy or tolerance of T cells might be induced by interaction with immature DCs, which do not express these co-stimulatory molecules, but do express tolerance-inducing molecules such as IL-10, B7-H1 and immunoglobulin-like transcript 3 (ILT3). This tolerogenic DC phenotype can be induced by exposure of DCs to IL-10, glucocorticoids or transforming growth factor-β (TGFβ). As its name suggests,

> “expression of GILZ by DCs treated with dexamethasone or IL-10 prevented them from stimulating T-cell proliferation”

GILZ expression is induced in DCs in response to glucocorticoids, as well as IL-10. So, the authors asked whether the induction of GILZ expression by DCs could explain the inhibitory effect of glucocorticoids and IL-10 on immune responses.

First, the authors confirmed that treatment of monocyte-derived human DCs with IL-10 or dexamethasone (a synthetic glucocorticoid) resulted in induction of GILZ expression, and inhibited the expression of CD80 and CD86 but stimulated the expression of B7-H1. Importantly, knockdown of GILZ gene expression, using small interfering RNA (siRNA), prevented the IL-10- or dexamethasone-induced phenotypic changes, whereas transfection of DCs with GILZ was sufficient to cause these changes.

In addition to modulating the phenotype of DCs, GILZ also affected their function. GILZ expression stimulated the production of IL-10 by DCs to the same extent as that achieved with dexamethasone, and it could inhibit chemokine production induced by CD40 ligand (CD40L). However, GILZ expression did not prevent all of the consequences of DC maturation, as it did not affect CD40L-induced inhibition of phagocytosis.

Consistent with its effect on DC maturation, the authors next showed that the expression of GILZ by DCs treated with dexamethasone or IL-10 prevented them from stimulating T-cell proliferation and interferon-γ release. Knockdown of GILZ with siRNA abolished this effect and restored a strong T-cell proliferative response.

Given that glucocorticoids are widely used to treat immune disorders that involve uncontrolled immune activation, the authors tested whether GILZ might be important for their mechanism of action. Indeed, GILZ expression was induced in circulating monocytes that were isolated from patients treated with glucocorticoids, and this impaired the ability of these cells to stimulate T cells.

So, a role for GILZ seems to be a common feature of immune control mediated by IL-10 and glucocorticoids, adding another level to our understanding of how DCs regulate adaptive immune responses.

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