The development of different population of dendritic cells (DCs) is controlled by cytokines, growth and differentiation factors as well as various transcription factors.1,2 The cytokines granulocyte-macrophage colony-stimulating factor (GM-CSF) and FLT3 ligand (FLT3L) support DC development by modulating the expression of multiple transcription factors in DC progenitors and DCs, including PU.1, E2–2, interferon-regulatory factor (IRF)4, IRF8, SPIB, basic leucine zipper transcription factor, ATF-like (BATF) and BATF3.3,4 In particular, GM-CSF activates the signal transducer and activator of transcription 5 (STAT5) and inhibits the FLT3L-dependent maturation of plasmacytoid dendritic cells (pDCs) by repressing IRF8.4

Cytokine inducible SH2-containing protein (CISH), a member of the suppressor of cytokine signaling (SOCS) protein family, has been shown to be induced in several hematopoietic cells by cytokines,5,6 but the functional link between CISH and DC development had never been investigated. Recently, we have demonstrated that CISH, which is not expressed in bone marrow cells, is significantly upregulated at late DC developmental stages. The levels of MHC Class I and co-stimulatory molecules were downregulated on the surface of developing DCs subjected to the CISH knockdown. The induction of CISH is involved in DC development as it inhibits the proliferation of DC precursors, allowing for their complete differentiation (Fig. 1). CISH is consistently upregulated by human T cells activated by interleukin (IL)-2 and is critical for both T-cell proliferation and survival upon the activation of T-cell receptor (TCR)-mediated signaling pathways.8 Conversely, our findings suggest that CISH negatively regulates cell proliferation during DC development by blocking STAT5 activation (Fig. 1). CISH is well known as a STAT5 target gene, while CISH negatively regulates STAT5 activation.9 We found that STAT5 expression and activation gradually increase during the early stages of DC development, but are suppressed by CISH at later stages, followed by the inhibition of cell proliferation (Fig. 1). According, the silencing of CISH led to STAT5 activation and promoted cell proliferation. These results suggest that CISH may have at least two different functions, that is, the regulation of differentiation or cell proliferation, depending on cell type and/or developmental stage. The induction of CISH plays a crucial role in the development of Type 1 DCs.

We further investigated the biological implications of CISH expression during DC development. The downregulation of MHC Class I molecules and other co-stimulatory molecules in DCs subjected to the knockdown of CISH suggested indeed that CISH might be involved in Th1 immune responses. In line with this hypothesis, CISH-depleted DCs produced significantly lower amounts of the Th1 cytokines IL-6, IL-12 and tumor necrosis factor α (TNFα) as compared with their control counterparts, while difference in the amounts of the Th2 cytokine IL-4 less pronounced. In a T-cell proliferation assay, CISH-depleted ovalbumin (OVA)-pulsed mature DCs were significantly impaired in their ability to stimulate OVA-specific CD8+ OT-I T cells as compared with control DCs, while the knockdown of CISH did not affect the ability of DCs to stimulate OVA-specific CD4+ OT-II T cells. Our results suggest therefore that CISH...
expression during the development of DCs is essential for TH1 polarization. The effector function of DCs in DC-based vaccination models were also impaired by the depletion of CISH. In particular, the levels of interferon γ (IFNγ) in the spleen and draining lymph nodes (DLNs) of OT-1 mice vaccinated with CISH-depleted OVA-pulsed DCs were significantly lower than those of OT-1 mice vaccinated with OVA-pulsed normal DCs. OVA-specific cytotoxic T lymphocytes (CTLs) were not properly induced in mice vaccinated with CISH-depleted DCs, resulting in the impairment of DC-based immunotherapy. These data suggest that CISH is essential for the activation of CD8+ T cells during DC-based immunotherapy. Overall, our findings indicate that the abundant expression of CISH during DC development is essential for the differentiation of TH1 DCs from bone marrow cells, and allows for the activation of antigen-specific CTLs during DC-mediated immunotherapy.

The risk of infectious diseases appears to be increased in people carrying mutant CISH alleles. This implies that CISH plays a pivotal role in the immune response against foreign invaders, but the underlying immunological mechanisms remain unclear. It has been proposed that CISH mutations may be accompanied by enhanced STAT5 activation, leading to an increase in regulatory T cells (Tregs), and hence to immunosuppressive effects that may enhance the susceptibility to infectious agents. Our findings suggest that the relatively high susceptibility to infectious diseases of patients bearing CISH mutations is at least in part due to an impaired induction of CTL responses by DCs. CISH−/− mice if available will surely provide a better understanding of the role of CISH in immune responses in vivo.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

References

1. Blander JM, Medzhitov R. Toll-dependent selection of microbial antigens for presentation by dendritic cells. Nature 2006; 440:808-12; PMID:16489357; http://dx.doi.org/10.1038/nature04596.
2. Geissmann F, Manz MG, Jung S, Sieweke MH, Mezal M, Ley K. Development of monocytes, macrophages, and dendritic cells. Science 2010; 327:656-61; PMID:20133564; http://dx.doi.org/10.1126/science.1178351.
3. Tissiaard R, Lee WL, Murphy TL, Mashayekhi M, Wunens KC, Abing JC, et al. Compensatory dendritic cell development mediated by BATF-IRF interactions. Nature 2012; 490:502-7; PMID:22992524; http://dx.doi.org/10.1038/nature11531.
4. Esashi E, Wang YH, Peng O, Qin XI, Liu YJ, Watowich SS. The signal transducer STAT5 inhibits plasmacytoid dendritic cell development by suppressing transcription factor IRF8. Immunology 2008; 28:509-20; PMID:18342552; http://dx.doi.org/10.1016/j.immu.2008.02.013.
5. Yoshimura A, Ohkubo T, Kiguchi T, Jenkins NA, Gilbert DJ, Copeland NG, et al. A novel cytokine-inducible gene CIS encodes an SH2-containing protein that binds to tyrosine-phosphorylated interleukin 3 and erythropoietin receptors. EMBO J 1995; 14:2816-26; PMID:7796808.
6. Lehtonen A, Matikainen S, Miettinen M, Julkunen I. Granulocyte-macrophage colony-stimulating factor (GM-CSF)-induced STAT5 activation and target-gene expression during human monocyte/macrophage differentiation. J Leukoc Biol 2002; 71:511-9; PMID:11867689.
7. Lehtonen A, Matikainen S, Miettinen M, Julkunen I. Granulocyte-macrophage colony-stimulating factor (GM-CSF)-induced STAT5 activation and target-gene expression during human monocyte/macrophage differentiation. J Leukoc Biol 2002; 71:511-9; PMID:11867689.
8. Li S, Chen S, Xu X, Sundstedt A, Paulsson KM, Anderson P, et al. Cytokine-induced Src homology 2 protein (CIS) promotes T cell receptor-mediated proliferation and prolongs survival of activated T cells. J Exp Med 2000; 191:985-94; PMID:10727460; http://dx.doi.org/10.1084/jem.191.6.985.
9. Matsumoto A, Seki Y, Kubo M, Ohtsuka S, Suzuki Y, A TAKEUCHI T, et al. CISH and susceptibility to infectious diseases. N Engl J Med 2010; 362:2092-101; PMID:20484391; http://dx.doi.org/10.1056/NEJMoa0905606.