the cognate antigen be even more efficient in this respect (as defended by some)[9]? We should not rush to embrace this latter hypothesis. Efficient secondary immune responses do not require high frequencies of memory T cells. Memory T cells maintained in the absence of cognate antigen are so efficient that a small number can mount potent secondary responses *in vivo*[11]. The persistence of cognate antigen, on the other hand, may lead to anergy or exhaustion[13]. The "window" in which optimal memory function is maintained and tolerance is avoided may be a very narrow one.

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Gonococci cause immunosuppression by engaging a coinhibitory receptor on T lymphocytes

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Gonococci that bind the coinhibitory receptor CEACAM1 appear to down-regulate the activation and proliferation of CD4$^+$ T cells. Such infection-induced immunosuppression helps explain why there is little specific immune response associated with gonococcal disease.

Gonorrhea is a commonly occurring sexually transmitted disease caused by *Neisseria gonorrhoeae* that typically does not result in protective immunity, despite an intensive inflammatory reaction[1]. The underlying mechanism for this is thought to be the extensive and rapid variation of important surface antigens—such as adhesive pili, lipooligosaccharides and the so-called opacity proteins (Opas)—which result in immunoevasion. However, gonorrhea is also believed to predispose individuals to HIV-1 and chlamydia infection, which suggests that gonococci might down-regulate local specific immune responses in a more direct manner. In this issue of *Nature Immunology*, Boulton and Gray-Owen show that gonococci—which bind carcinoembryonic antigen–related cellular adhesion molecule 1 (CEACAM1) on CD4$^+$ T cells—can down-regulate the activation and proliferation of these infected cells, and argue that gonococci themselves may suppress the typical immune response associated with bacterial infection[2].

N. gonorrhoeae as well as *N. meningitidis*—which can cause systemic diseases, including meningitis—are capable of expressing up to 11 different Opa proteins. This occurs in a phase-variable manner so that expression of each gene can go in- or out-of-frame as a result of frequent variations in the number of penta-CTCTT repeats located at the beginning of the coding sequence. When human volunteers are inoculated with gonococci that are expressing all the *opa* genes out-of-frame, Opa-expressing variants are constantly selected soon after infection, which suggests a role for these proteins in the successful gonococci infection process[3]. The Opa proteins are adhesins that mediate bacterial uptake into epithelial and endothelial cells, as well as into phagocytosing leukocytes, *via* ligand binding. The large majority of Opa proteins in both gonococci and meningococci can bind various members of the CEACAM (also known as the CD66) receptor family[4,5]. Bacterial binding to CEACAM on epithelial and endothelial cells induces invasion of gonococci and transepithelial migration. In neutrophils, Opa-CEACAM interactions promote opsonin-independent phagocytosis.

The functions of CEACAM1 on epithelial, endothelial and leukocytic cells include homophilic adhesion, tumor suppression and the regulation of cell adhesion and proliferation. It also acts as a receptor for E-selectin, pathogenic and commensal *Neisseria* and *Haemophilus influenzae* and murine corona viruses[6]. CEACAM1 is the only member of the CEACAM receptor family that is expressed on human lymphocytes, and its surface expression correlates with the activation state of the lymphocyte[7]. Boulton and Gray-Owen infected human CD4$^+$ T cells with genetically defined gonococcal strains that expressed either Opa$_{52}$, which binds CEACAM1, or Opa$_{50}$, which binds heparan sulphate proteoglycans[2]. They show that Opa$_{50}$-expressing bacteria increase the proportion of CD4$^+$ T cells that express the early activation marker CD69. Interestingly, there was no such increase in the proportion of CD69-expressing effector cells when the CD4$^+$ T cells were infected with an Opa$_{52}$-expressing strain. The down-regulating effect of Opa$_{52}$ gonococci on effector cells was accompanied by a reduced proliferative response by CD4$^+$ T lymphocytes to activation stimuli such as interleukin 2 (IL-2) or CD3 ligation. The immunosuppressive effects seen with CEACAM1-binding gonococci were similar to those obtained with CEACAM-specific antibodies, which suggests that CEACAM1 ligation was responsible for the immunosuppressive effects observed.

The activation of CD4$^+$ T lymphocytes by Opa$_{50}$-expressing gonococci is probably induced by pathogen-associated molecular patterns (PAMPS) such as lipooligosaccharides, which can activate immune responses *via* NF-κB. Other gonococcal surface molecules may also act as direct or indirect immunostimulators, rather than immunsuppressors, of T lymphocytes. For example, the neisserial outer membrane porin proteins can activate T cells by inducing CD80 (also known as B7-2), which is a costimulatory molecule, on B cells[8]. Boulton and Gray-Owen show that gonococci expressing adhesive pili stimulate

lymphocyte proliferation even better than pilus-deficient Opa_{50}-expressing gonococci[2]. Gonococcal pili interact with CD46—a complement regulatory receptor for C3b, as well as a receptor for several pathogens[9], that acts as a potent costimulatory molecule for human T cells—inducing strong T cell proliferation[10]. It is therefore possible that the gonococcal pili influence lymphocyte proliferation by interaction with CD46. Other immunoactivation pathways have yet to be investigated for *Neisseria*-infected T lymphocytes.

How can T cell growth be suppressed by CEACAM1 ligation? The mechanism proposed by Boulton and Gray-Owen[2] is based on findings that the cytoplasmic domain of CEACAM1 contains tyrosine residues that potentially interact with protein tyrosine kinases of the Src family as well as an immunoreceptor tyrosine inhibition motif (ITIM) interacting with the protein tyrosine phosphatases SHP-1 and SHP-2[11]. Activation of the T cell receptor (TCR) would then activate Src kinase, allowing tyrosine phosphorylation of CEACAM1. Ligation of CEACAM1 by Opa, however, would allow recruitment of SHP-1 and SHP-2 to ITIM, thereby increasing the activation threshold for T lymphocytes by dephosphorylating CEACAM1 (**Fig. 1**). Boulton and Gray-Owen show convincingly that CEACAM1 ligation to Opa_{52} induces SHP-1 and SHP-2 to bind this receptor, and that binding is dependent on TCR activation (*via* ligation of CD3ε).

Thus, CEACAM1-binding pathogenic *Neisseria* tilts the delicate balance between costimulatory and coinhibitory signals during T cell activation to favor immunosuppression. Even though this is the first example of immunosuppression caused by bacterial engagement of a coinhibitory receptor, bacterial pathogens may use other strategies to down-regulate the immune system. For example, upon infection, *Salmonella typhimurium* activates the production of nitric oxide (NO). NO is normally induced by the innate immune response pathway that involves IL-12, natural killer cells and interferon-γ production by activated macrophages[12]. After immunization with an attenuated strain of *S. typhimurium*, murine splenocytes showed a profoundly suppressed capacity to mount an *in vitro* antibody plaque-forming cell response to sheep erythrocytes[13]. Evidence indicates that this suppression was mediated by NO, as the *in vitro* addition of NG-monomethyl-L-arginine abrogated suppression[13]. Because many pathogens will induce NO, this type of NO-mediated immunosuppression might be quite general.

The destruction and processing of bacteria by activated macrophages facilitates the presentation of antigens to T cells and thereby promotes the induction of specific immunity. PhoP-PhoQ is a two-component regulatory system that governs virulence, mediates adaptation to Mg^{2+}-limiting environments and regulates numerous cellular activities in Gram-negative bacterial species. It consists of the inner membrane sensor PhoQ and the cytoplasmic regulator PhoP. An *in vitro* antigen-processing system showed that *phoP*-regulated gene products could decrease the processing and presentation of *S. typhimurium* antigens, demonstrating a role for this virulence locus in inhibition of the induction of specific immunity[14].

Most bacteria activate innate immune responses that involve the induction of cytokines required for adaptive immune responses. Some bacterial pathogens use effector proteins delivered by a dedicated type III secretion system to block the signaling pathway, which leads to activation of the transcription factor NF-κB. One example of this is *Yersinia* YopP-YopJ. *Yersinia* is also able to secrete a powerful phosphotyrosine phosphatase YopH, which, in macrophages, plays an antiphagocytic role by dephosphorylating several focal adhesion proteins. YopH can, however, also be delivered into both T and B lymphocytes, where it is thought to suppress activation by inhibiting phophorylation of antigen receptor complexes[15].

Besides the examples given above and in this issue of *Nature Immunology*[2], there are few studies on the modulation of lymphocyte function by bacterial pathogens. There are still many unanswered questions. For instance, to what extent do the *in vitro* experiments described by Boulton and Gray-Owen[2] reflect the situation that occurs *in vivo* in infected patients. Will, for example, a sufficient fraction of T lymphocytes be interacting with Opa-expressing bacteria or bacterial fragments to cause an overall immunosuppressive effect? In the end, the immune response in human volunteers infected with CEACAM1-binding bacteria will have to be compared with the response generated by gonococci that bind heparan sulphate and not CEACAM1.

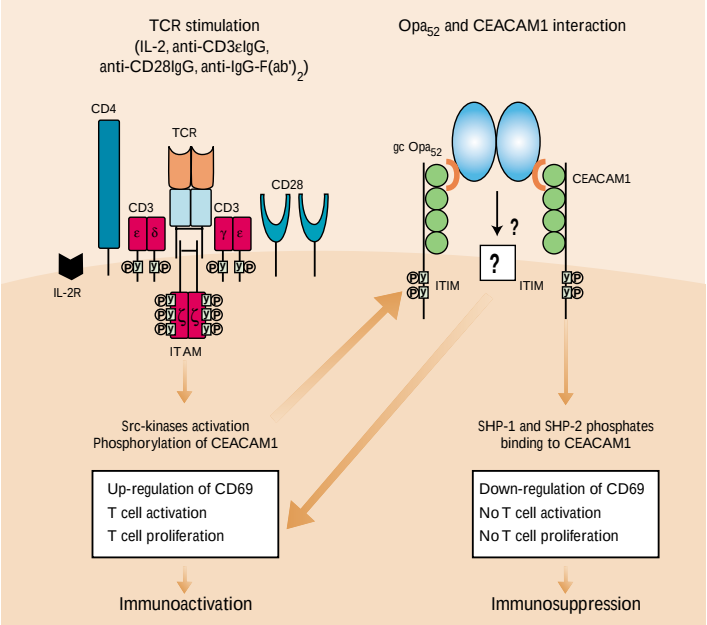

Figure 1. Expression of the bacterial surface protein Opa_{52} inhibits activation and proliferation of *Neisseria*-infected $CD4^+$ T lymphocytes. Immunosuppression is mediated by interactions between Opa_{52} and the CEACAM1 receptor, which allows the ITIM motif on CEACAM1 to bind tyrosine SHP-1 and SHP-2 phosphatases. This alters the delicate balance between costimulatory and coinhibitory signals. Other surface molecules expressed by gonococci will directly or indirectly immunostimulate, rather than immunosuppress, T cell activation. Those other immunoactivation pathways have not yet been investigated for *Neisseria*-infected T lymphocytes.

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