The price of the CD27–CD70 costimulatory axis: you can't have it all

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T cells require costimulatory signals for optimal proliferation, differentiation, and survival and thus to induce protective immune responses. Recent data, however, show that during chronic lymphocyte choriomeningitis virus (LCMV) infection, triggering of the costimulatory receptor CD27 by its ligand CD70 impedes neutralizing antibody production and leads to viral persistence. Thus, while being crucial for the induction of some adaptive effector pathways, costimulation may block the development of others. Pathogens may exploit this Achilles' heal to achieve persistence.

LCMV and CD27

Proper immunity against pathogenic infection depends on the well-orchestrated cooperation of innate and adaptive arms of the immune system. In the optimal situation, this leads to eradication of the pathogen and long-term memory that protects the host against future infection. Toll-like receptors, antigen receptors, costimulatory molecules, soluble mediators, and many other molecules are all important for the initiation, sustenance, and regulation of this intricate process. However, millions of years of evolutionary pressure have also enabled pathogens to develop their own sophisticated tools to manipulate the mammalian defense system to potentiate their survival and reproduction in the host. One example of this, described in an article by Matter et al. in a recent issue of the *JEM*, suggests a new role for the tumor necrosis factor (TNF) receptor superfamily member CD27 in the clearance of persistent LCMV infections (1).

The authors report that CD27 signaling is not beneficial for the course of the immune response against LCMV, but rather has a detrimental effect on protective antiviral immunity. This is a new and unexpected finding, as CD27 signaling has so far been regarded as an important positive immune regulator for the formation and function of effector and memory T cells. In the absence of CD27, for example, the magnitude of T and B cell effector responses is reduced compared with responses in wild-type animals (2). Likewise, transgenic overexpression of CD70 augments the formation of effector T cells leading to enhanced protection against non-immunogenic tumors (3). In the new study, however, CD27-deficient mice were better protected against infection with a high dose of LCMV than were wild-type mice, because they were able to generate virus-specific neutralizing antibodies (nAbs). As shown previously by this group, the primary cytotoxic T cell–dependent response to this virus is normal in $CD27^{-/-}$ mice (4). The intriguing finding that $CD27^{-/-}$ mice developed protective nAbs is explained by the fact that signals transmitted through CD27 during LCMV infection in wild-type mice lead to the destruction of splenic lymphoid architecture. The authors show that LCMV infection in wild-type mice, but not in $CD27^{-/-}$ mice, causes the destruction of germinal centers and the marginal zone, which are required for the development of nAbs. This destruction is attributed to the production of interferon (IFN)-γ and TNF-α by activated $CD4^+$ T cells, which depends on the expression of CD27 on these cells (Fig. 1). Blocking CD70 in wild-type mice also resulted in the production of nAbs and resistance against an otherwise persistent strain of LCMV (1). Based on these findings, the authors suggest that blocking CD27 signaling could be a novel approach for treating clinically relevant chronic infections such as HIV and hepatitus C virus.

CD27 signals: bad for B cells

The splenic destruction wreaked by LCMV infection in mice fits well with previous studies on the effects of CD27–CD70 signaling. Chronic activation of CD27 through constitutive expression of CD70, for example, leads to the demise of the B cells both in the bone marrow and secondary lymphoid organs (5). Consistent with this, a conspicuous finding in these CD70 transgenic mice is the early loss of the splenic marginal zone (6), a structure comprising a tight organization of specialized macrophages and B cells that is required for a protective immune response against encapsulated bacteria and viruses (7–10).

The spleen is both a major site of early LCMV replication and the compartment in which cytotoxic T cell and antibody responses against the virus are initiated—both responses that contribute to viral clearance (11–13). Although it is interesting to speculate that marginal zone B cells and macrophages are uniquely important for the development of LCMV-specific nAbs, it is important to note that LCMV infection is also accompanied by loss of follicular structure and germinal center formation (1, 14). An intriguing interdependency seems to exist between macrophages in the marginal zone and B cells, as B cell depletion leads to gradual loss of macrophages in the marginal zone (6). The organization of marginal zone B cells in turn depends on the presence of marginal zone macrophages (15). During LCMV infection, follicular B cells remain present,

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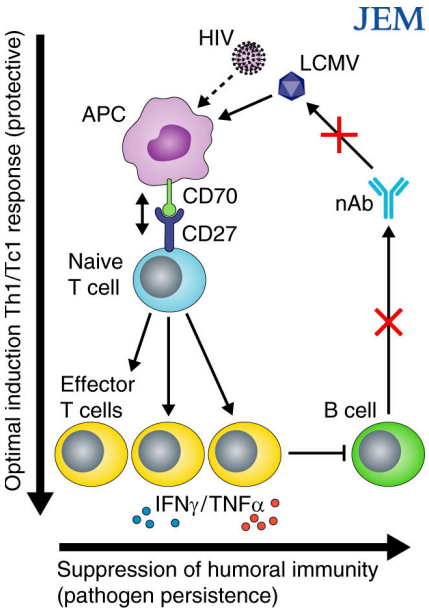

Figure 1. Strong effector cell formation and protective antiviral antibody responses may be mutually exclusive during chronic viral infection. In this model, strong CD27–CD70-induced signals trigger robust Th1/Tc1 effector cell responses, including the production of IFN-γ and TNF. If these cytokines are produced in large quantities, they can induce the destruction of lymphoid organ organization and thus impair B cell activation. This consequently impairs the production of nAbs that are required to efficiently eliminate the pathogen.

but both marginal zone macrophages and marginal zone B cells disappear, although the cause of their mutual disappearance is not yet known.

During the initial phase of the immune response, antigen presenting cells (APCs) up-regulate a large number of costimulatory ligands belonging to both the immunoglobulin superfamily (most prominently the B7 proteins) and the TNF family. Taking into account the potential plethora of available coactivating ligands, it seems surprising that during LCMV infection elimination of only the CD27–CD70 interaction has such a drastic effect on B cell maintenance. Several features of CD27 expression and function may contribute to this apparently dominant role for CD27 during LCMV infection. First, as pointed out by Croft (16), members of the TNF-R family may function in a sequential fashion with CD27 being activated early in the immune response. This role of CD27 early after infection might explain why its deletion has such a dramatic effect on the course of the antiviral immune response. Second, both in vitro and in vivo CD27 signaling has a strong effect on the differentiation of naive T cells into IFN-γ–secreting T helper (Th)1 effector cells. This effect appears to be due to the ability of CD27 to sensitize naive T cells to Th1 differentiation-inducing signals such as interleukin-12 (unpublished data). As mentioned previously, IFN-γ is known to contribute to the destruction of splenic architecture. Third, although induction of CD70 expression in vivo is hard to demonstrate using pathogens such as influenza virus, LCMV was found to induce CD70 expression on a substantial number of both T and B cells during the course of the infection (1). It could well be that CD70 expression is differently regulated in various infections. This could depend on the tropism of the virus for cells of the immune system and/or recognition of the virus by immune cells. Moreover, it remains to be clarified whether other costimulatory systems, especially of the TNF–TNF receptor pathway, contribute to LCMV-induced B cell depletion. Of special interest is the 4-1BB system, as mice that chronically overexpress 4-1BB ligand display a B cell depletion phenotype similar to that seen in CD70 transgenic mice (17).

Other chronic infections

Protective immunity against LCMV and other noncytolytic viruses depends on rapid induction of strong Th1/Tc1 responses and the production of nAbs, but these immune defense mechanisms are actively circumvented by many viruses. Some viruses, such as HIV and measles, induce a permanent or transient immunodepression, preventing Th1 induction, for example, by suppressing interleukin-12 production (18). The induction of Th1/Tc1 immune responses promotes immunity against these viruses, probably at least in part by activating CD27–CD70 signaling. However, the study by Matter et al. raises the possibility that this signaling could also negatively affect the development of essential nAbs (1).

Infection with the *Leishmania* parasite provides an interesting parallel with LCMV infection in that *Leishmania* infections are also associated with the destruction of the splenic marginal zone. In this system, marginal zone destruction is caused by a TNF-α–mediated decrease in the production of the chemokines CCL19 and CCL21, which are important for marginal zone maintenance (19, 20). CD70 has been shown to be up-regulated on dendritic cells from *Leishmania*-infected mice (21). However, whether CD70 expression and marginal zone destruction during *Leishmania* infection are causally linked is not yet known. It is also unclear whether the production of nAbs against *Leishmania* is precluded by the destruction of the marginal zone. Conspicuously, patients with visceral Leishmaniasis are known to suffer from secondary bacterial infections (22) and it would be interesting to determine if this could be caused by defects in the formation of nAbs against these bacteria.

Th1 responses are required for the successful eradication of the *Leishmania* pathogen, whereas Th2 responses are detrimental and lead to nonhealing disease. It will therefore be interesting to investigate whether CD27-mediated costimulation, which is beneficial for immunity against *Leishmania* as it propagates Th1/Tc1 responses, can also be detrimental caused by inhibition of nAb production.

The B cell defects in studies of LCMV infection bear a striking resemblance to the B cell dysfunctions observed in HIV-infected people. Architecture of both germinal centers (23, 24) and splenic marginal zones is disturbed in individuals infected with HIV (25). Moreover, the ability to produce nAbs is rapidly lost in most people after HIV infection, but is maintained in chimpanzees that harbor the virus but do not develop disease (26). Intriguingly, HIV-infected people, but not monkeys, display a chronic activation of the immune system, including increased expression of CD70 on $CD8^+$ T cells (27–29). Combining the mouse, monkey,

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and human data, it is tempting to suggest that the CD27–CD70 costimulatory pathway is instrumental in generating B cell dysfunction and in causing the absence of sustained nAb production after HIV infection. It will be interesting to investigate if people with long-term asymptomatic HIV infections who have stable nAb titers differ in CD27–CD70 expression and/or function compared with patients that progress to AIDS. Moreover, for persistent infections in humans, such as HIV and hepatitus C virus, specific blockade of the CD27–CD70 pathway may tip the balance, as in chronic LCMV, to favor a protective humoral immune response.

Evolutionary pressure

The surprising finding that the absence, rather than the presence, of an immune receptor such as CD27 is beneficial in the fight against an invading pathogen illustrates the challenges with which the mammalian immune system has to cope. The immune system has to find the optimal balance between humoral and cellular responses that is sufficient in both quality and quantity to eradicate the invading pathogen without causing immune pathology or self-reactivity. Although a strong signal through CD27 seems like an appropriate response to viral infection in that it enhances Th1/Tc1 responses, it apparently has a major drawback in its tendency to destroy lymphoid organization and thus obstruct nAb production. In a recent review, Hedrick pointed out that during their coevolution, pathogens have been at least as creative in finding ways to deal with the complex adaptive immune system of their hosts as their hosts' immune systems have been in finding ways to fend them off (30). From this perspective, viruses like LCMV may "deliberately" use the CD27–CD70 axis to overstimulate one arm of the immune response to weaken the other. Conversely, it is also possible that this is not an evolutionary trick of LCMV, but is simply part of the collateral immune damage that is also inflicted by other pathogens. These issues are important to address, as they not only provide us with more insight into the physiology of the immune system and that of the pathogen, but may also lead us to new clinical approaches to treat infection.

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REFERENCES

1. Matter, M., B. Odermatt, H. Yagita, J.M. Nuoffer, and A.F. Ochsenbein. 2006. Elimination of chronic viral infection by blocking CD27 signaling. *J. Exp. Med.* 203: 2145–2155.
2. Hendriks, J., L.A. Gravestein, K. Tesselaar, R.A. van Lier, T.N. Schumacher, and J. Borst. 2000. CD27 is required for generation and long-term maintenance of T cell immunity. *Nat. Immunol.* 1:433–440.
3. Arens, R., K. Schepers, M.A. Nolte, M.F. van Oosterwijk, R.A. van Lier, T.N. Schumacher, and M.H. van Oers. 2004. Tumor rejection induced by CD70-mediated quantitative and qualitative effects on effector $CD8^+$ T cell formation. *J. Exp. Med.* 199:1595–1605.
4. Matter, M., S. Mumprecht, D.D. Pinschewer, V. Pavelic, H. Yagita, S. Krautwald, J. Borst, and A.F. Ochsenbein. 2005. Virus-induced polyclonal B cell activation improves protective CTL memory via retained CD27 expression on memory CTL. *Eur. J. Immunol.* 35:3229–3239.
5. Arens, R., K. Tesselaar, P.A. Baars, G.M. van Schijndel, J. Hendriks, S.T. Pals, P. Krimpenfort, J. Borst, M.H. van Oers, and R.A. van Lier. 2001. Constitutive CD27/CD70 interaction induces expansion of effector-type T cells and results in IFNgamma-mediated B cell depletion. *Immunity.* 15: 801–812.
6. Nolte, M.A., R. Arens, M. Kraus, M.H. van Oers, G. Kraal, R.A. van Lier, and R.E. Mebius. 2004. B cells are crucial for both development and maintenance of the splenic marginal zone. *J. Immunol.* 172:3620–3627.
7. Muller, S., L. Hunziker, S. Enzler, M. Buhler-Jungo, J.P. Di Santo, R.M. Zinkernagel, and C. Mueller. 2002. Role of an intact splenic microarchitecture in early lymphocytic choriomeningitis virus production. *J. Virol.* 76: 2375–2383.
8. Seiler, P., P. Aichele, B. Odermatt, H. Hengartner, R.M. Zinkernagel, and R.A. Schwendener. 1997. Crucial role of marginal zone macrophages and marginal zone metallophils in the clearance of lymphocytic choriomeningitis virus infection. *Eur. J. Immunol.* 27:2626–2633.
9. Fehr, T., C. Lopez-Macias, B. Odermatt, R.M. Torres, D.B. Schubart, T.L. O'Keefe, P. Matthias, H. Hengartner, and R.M. Zinkernagel. 2000. Correlation of anti-viral B cell responses and splenic morphology with expression of B cell-specific molecules. *Int. Immunol.* 12:1275–1284.
10. Mebius, R.E., M.A. Nolte, and G. Kraal. 2004. Development and function of the splenic marginal zone. *Crit. Rev. Immunol.* 24: 449–464.
11. Ochsenbein, A.F., T. Fehr, C. Lutz, M. Suter, F. Brombacher, H. Hengartner, and R.M. Zinkernagel. 1999. Control of early viral and bacterial distribution and disease by natural antibodies. *Science.* 286:2156–2159.
12. Seiler, P., M.A. Brundler, C. Zimmermann, D. Weibel, M. Bruns, H. Hengartner, and R.M. Zinkernagel. 1998. Induction of protective cytotoxic T cell responses in the presence of high titers of virus-neutralizing antibodies: implications for passive and active immunization. *J. Exp. Med.* 187:649–654.
13. Zinkernagel, R.M., A. LaMarre, A. Ciurea, L. Hunziker, A.F. Ochsenbein, K.D. McCoy, T. Fehr, M.F. Bachmann, U. Kalinke, and H. Hengartner. 2001. Neutralizing antiviral antibody responses. *Adv. Immunol.* 79: 1–53.
14. Odermatt, B., M. Eppler, T.P. Leist, H. Hengartner, and R.M. Zinkernagel. 1991. Virus-triggered acquired immunodeficiency by cytotoxic T-cell-dependent destruction of antigen-presenting cells and lymph follicle structure. *Proc. Natl. Acad. Sci. USA.* 88:8252–8256.
15. Karlsson, M.C., R. Guinamard, S. Bolland, M. Sankala, R.M. Steinman, and J.V. Ravetch. 2003. Macrophages control the retention and trafficking of B lymphocytes in the splenic marginal zone. *J. Exp. Med.* 198: 333–340.
16. Croft, M. 2003. Co-stimulatory members of the TNFR family: keys to effective T-cell immunity? *Nat. Rev. Immunol.* 3:609–620.
17. Zhu, G., D.B. Flies, K. Tamada, Y. Sun, M. Rodriguez, Y.X. Fu, and L. Chen. 2001. Progressive depletion of peripheral B lymphocytes in 4-1BB (CD137) ligand/I-Ealpha)-transgenic mice. *J. Immunol.* 167: 2671–2676.
18. Trinchieri, G. 1997. Function and clinical use of interleukin-12. *Curr. Opin. Hematol.* 4:59–66.
19. Ato, M., H. Nakano, T. Kakiuchi, and P.M. Kaye. 2004. Localization of marginal zone macrophages is regulated by C-C chemokine ligands 21/19. *J. Immunol.* 173: 4815–4820.
20. Engwerda, C.R., M. Ato, S.E. Cotterell, T.L. Mynott, A. Tschannerl, P.M. Gorak-Stolinska, and P.M. Kaye. 2002. A role for tumor necrosis factor-alpha in remodeling the splenic marginal zone during *Leishmania donovani* infection. *Am. J. Pathol.* 161:429–437.
21. Akiba, H., Y. Miyahira, M. Atsuta, K. Takeda, C. Nohara, T. Futagawa, H. Matsuda, T. Aoki, H. Yagita, and K. Okumura. 2000. Critical contribution of OX40 ligand to T helper cell type 2 differentiation in experimental leishmaniasis. *J. Exp. Med.* 191:375–380.
22. Andrade, T.M., E.M. Carvalho, and H. Rocha. 1990. Bacterial infections in patients with visceral leishmaniasis. *J. Infect. Dis.* 162:1354–1359.
23. Koopman,G., P.C. Wever, M.D. Ramkema, F. Bellot, P. Reiss, R.M. Keehnen, I.J. Ten

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Berge, and S.T. Pals. 1997. Expression of granzyme B by cytotoxic T lymphocytes in the lymph nodes of HIV-infected patients. *AIDS Res. Hum. Retroviruses*. 13:227–233.
24. Koopman, G., and S.T. Pals. 1992. Cellular interactions in the germinal center: role of adhesion receptors and significance for the pathogenesis of AIDS and malignant lymphoma. *Immunol. Rev.* 126:21–45.
25. Wilkins, B.S., Z. Davis, S.B. Lucas, G. Delsol, and D.B. Jones. 2003. Splenic marginal zone atrophy and progressive CD8+ T-cell lymphocytosis in HIV infection: a study of adult post-mortem spleens from Cote d'Ivoire. *Histopathology*. 42:173–185.
26. Beaumont, T., S. Broersen, A. van Neunen, H.G. Huisman, A.M. de Roda Husman, J.L. Heeney, and H. Schuitemaker. 2000. Increased neutralization sensitivity and reduced replicative capacity of human immunodeficiency virus type 1 after short-term in vivo or in vitro passage through chimpanzees. *J. Virol.* 74:7699–7707.
27. Hazenberg, M.D., D. Hamann, H. Schuitemaker, and F. Miedema. 2000. T cell depletion in HIV-1 infection: how CD4+ T cells go out of stock. *Nat. Immunol.* 1:285–289.
28. Gougeon, M.L., H. Lecoeur, F. Boudet, E. Ledru, S. Marzabal, S. Boullier, R. Roue, S. Nagata, and J. Heeney. 1997. Lack of chronic immune activation in HIV-infected chimpanzees correlates with the resistance of T cells to Fas/Apo-1 (CD95)-induced apoptosis and preservation of a T helper 1 phenotype. *J. Immunol.* 158:2964–2976.
29. Wolthers, K.C., S.A. Otto, S.M. Lens, D.N. Kolbach, R.A. van Lier, F. Miedema, and L. Meyaard. 1996. Increased expression of CD80, CD86 and CD70 on T cells from HIV-infected individuals upon activation in vitro: regulation by CD4+ T cells. *Eur. J. Immunol.* 26:1700–1706.
30. Hedrick, S.M. 2004. The acquired immune system: a vantage from beneath. *Immunity*. 21:607–615.

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