IL-1 β Strikingly Enhances Antigen-Driven CD4 and CD8 T-Cell Responses

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Protective immune response requires massive expansion of antigen-triggered naïve cells, extensive differentiation into effector cells, migration of effectors into the periphery, and generation of a functional memory compartment. IL-1 β strikingly enhances expansion of antigen-primed CD8 and CD4 T cells in vivo. Its T-cell expansion in lymph nodes and spleen was direct, requiring that the stimulated T cells express IL-1R1. Immunization in the presence of IL-1 β increases the frequency of IL-17- and IFN- γ -producing cells among primed CD4 cells and the frequency of granzyme B-expressing and IFN- γ -producing cells and of cytotoxic cells among primed CD8 cells. IL-1 β -induced increase in the number of the activated CD4 and CD8 cells and augmented differentiation of the antigen-triggered T cells is very pronounced in liver and lungs. CD4 and CD8 cells primed in the presence of IL-1 β display augmented cell number and enhanced cytokine production when rechallenged 2 mo after priming with antigen and lipopolysaccharide (LPS). In five in vivo models, IL-1 β enhanced the protective value of weak vaccines. Preliminary analysis of in vivo gene expression in CD4 cells stimulated with IL-1 β revealed that IL-1 β caused gene expression changes consistent with the up-regulation of pathways involved in cell replication, cell survival, and enhanced energy metabolism. Thus, IL-1 β enhances antigen-primed CD4 and CD8 T-cell expansion, differentiation, and migration to the periphery and memory, the specific functions required for generation of effective protective immune responses.

Charles Janeway's emphasis that pathogen-sensing was central to the development of robust immune responses (Janeway 1989) built on the recognition that microbial products could be used to strikingly enhance specific antibody responses (Freund et al. 1953). Matzinger emphasized that endogenous products, as danger signals, played an important role in this process (Matzinger 1994). Indeed, the discovery that Toll acted as an important element in the capacity of flies to make protective responses against fungal infections (Lemaitre et al. 1996) was consistent with this idea since the ligand for Toll was an endogenous product, proteolytically cleaved Spätzle (Morisato and Anderson 1994). Further, the cytosolic domain of Toll and the TLRs are homologous to that of IL-1 β (Bowie and O'Neill 2000a) raising the possibility that IL-1 β and its homologs might play a central role in the enhancement of immune responses in vertebrates.

We became interested in the possible roles that cytokines might play in enhancing immune responses based on our studies of their effects on responses of naïve CD4 T cells in vitro (Ben-Sasson et al. 2000). We conducted a screen of the capacity of a wide range of cytokines to enhance the antigen-driven expansion of T-cell receptor transgenic CD4 T cells transferred to syngeneic recipients (Ben-Sasson et al. 2009). This screen revealed that IL-1 α and IL-1 β potently enhanced such antigen-driven responses and encouraged us to explore the effects of IL-

1 β in greater detail, both to understand the principles underlying its stimulatory activity and to explore the possibility of their application in enhancing protective immunity induced by vaccines.

We reported that IL-1 β acted directly on antigen-specific CD4 T cells to enhance their expansion and to promote their differentiation, particularly into IL-17-producing effector T cells. Our results indicated that IL-1 β enhanced both survival and proliferation of the responding cells, although the survival effect seemed to dominate (Ben-Sasson et al. 2009). We subsequently showed that IL-1 β exerted similar effects on antigen-responsive CD8 T cells (Ben-Sasson et al. 2013).

Here we have examined a series of functions that should be important in enhancing T-cell responses. Thus, an efficient protective adaptive immune response should require that the antigen-recognizing T cells undergo massive expansion, that they differentiate into efficient effector cells, that they migrate to the periphery to encounter the invading pathogen, and that they differentiate into long-term memory cells.

We show that IL-1 β mediates all these functions on both antigen-specific CD4 and CD8 T cells. In some instances, such as the expansion of these cells in secondary lymphoid organs, expression of IL-1 receptors only on the responding T cell is sufficient for the response but for other functions, such as traffic to, retention in, and/or

expansion in tissues, expression of IL-1R1 by other cells is required as it is for the differentiation of CD8 T cells to express granzyme B- and be capable of producing IFN- γ . We further show that IL-1 used with “weak” vaccines can enhance their protective capacity.

RESULTS

IL-1 β Enhances Responses of CD4 and CD8 T Cells to Their Cognate Antigen

To test the effect of IL-1 β on antigen-driven expansion of CD8 T cells and to compare such expansion to that of CD4 T cells, we transferred 10^4 lymph node cells from B6 OT-I TCR transgenic Rag1 $^{-/-}$ donors and B6 OT-II TCR transgenic Rag1 $^{-/-}$ donors to C57BL/6 mice that express GFP under the direction of the ubiquitin C promoter (UBC-GFP mice). The recipients were immunized

subcutaneously with 1 mg ovalbumin (OVA) together with 25 μ g LPS. They did or did not receive IL-1 β over a 5-d period (doses varying from 1.5 μ g on days 1, 3, and 5 to 2 μ g/d beginning 24 h after immunization). IL-1 β administration increased the number of cells in the lymph nodes and spleen and caused a striking augmentation in the frequency of transgenic cells in these lymphoid organs resulting in profound increase in the number of antigen-stimulated CD4 and CD8 cells 7 d after immunization. Figure 1 illustrates IL-1 β -mediated enhancement of antigen-driven expansion of OT-I cells in the spleen of recipient animals.

When CD45.1 OT-I and OT-II cells were transferred into IL-1R1 $^{-/-}$ CD45.2 recipients, the degree of IL-1 β -mediated enhancement of antigen-driven expansion was similar to that observed in wild-type (WT) mice in both lymph nodes and spleens (Fig. 2), implying that the bulk of the IL-1-mediated enhancement of antigen-stimulated

Figure 1. IL-1 enhances antigen-driven CD8 T-cell responses. 10^4 OT-I cells were injected into UBC-GFP C57BL/6 mice. Mice were immunized subcutaneously with OVA + LPS with or without IL-1 β . Seven days after priming, the frequency of splenic GFP $^{+}$ CD8 $^{+}$ OT-I cells among the CD8 $^{+}$ cells was determined. Results are presented as the percentage of GFP $^{+}$ CD8 $^{+}$ OT-I cells in the CD8 $^{+}$ population.

Figure 2. IL-1 augments the expansion of antigen-primed OT-I and OT-II cells in IL-1R1^{-/-} recipients. 10⁴ CD45.1 OT-I and 10⁴ CD45.1 OT-II cells were injected into CD45.2 IL-1R1^{-/-} C57BL/6 mice. Mice were immunized with OVA plus LPS with or without IL-1. Seven days after priming, cells were analyzed for number of OT-I and OT-II cells.

CD4 and CD8 T-cell priming required the expression of the IL-1 receptor on the antigen-responding T cells and that IL-1 receptor expression on other cells played only a limited role in the IL-1 β -enhanced expansion in lymph node and spleen. Furthermore, the IL-1 β -enhanced response of OT-I cells transferred to IL-1R1^{-/-} B6 recipients was not increased by the cotransfer of a similar number of CD4 OT-II cells (Ben-Sasson et al. 2013). Thus, IL-1 β enhancement of antigen-driven expansion of CD8 T cells in secondary lymphoid organs is a direct effect on the responding T cells and does not depend on “help” from CD4 T cells.

IL-1 β Causes Massive Increase in the Frequency of OT-I and OT-II Cells in Liver and Lung in Response to Immunization

OT-I and OT-II cells were transferred into UBC-GFP recipients that were immunized with OVA plus LPS with or without IL-1 β . Seven days after immunization, the total number of cells in the liver and lung was strikingly increased by coadministration of IL-1 β . In addition, IL-1 β caused a massive increase in the frequency of OT-I and OT-II cells in both organs. Indeed, even in mice that received only 10⁴ OT-I and OT-II cells, these cells now constituted the great majority of total CD8 within these organs and a substantial proportion of the CD4 cells. The results for expansion in the liver are shown in Figure 3.

As already noted, the IL-1 β -mediated increase in number of responding OT-I and OT-II cells in lymph node and spleen was independent of IL-1R1 expression in the non-OT-I and non-OT-II cells. In contrast, the number of OT-I and OT-II cells in liver and lung of immunized IL-1R1^{-/-} recipients treated with IL-1 β was far less than in identically treated WT recipients (Fig. 4), implying the need for IL-1 receptors on cells other than the responding T cells for entry, retention or expansion of these cells in nonlymphoid organs.

This requirement for IL-1 β responsiveness extends to the entry/retention/expansion of OT-I cells in immune responses in which exogenous IL-1 β was not provided. The frequency of OT-I cells in IL1R1^{-/-} recipient mice that were immunized with OVA plus LPS without exogenous IL-1 β was considerably reduced in comparison to that in WT recipients. These results indicate that IL-1, whether endogenous or administered, plays a central role in migration, expansion, or retention of recently primed effector or effector/memory CD8 T cells in nonlymphoid organs.

IL-1 β Enhances Effector Function of CD4 and CD8 T Cells in Response to Antigen Stimulation

Immunization of mice that received OT-I cells plus OT-II cells with OVA plus LPS caused few OT-I or OT-II cells residing in the lymph nodes and spleen to develop the capacity to produce effector cytokines or to express granzyme B. Addition of IL-1 β caused a striking increase in the proportion of OT-I cells that do express granzyme B and in the fraction of these cells that produced IFN- γ in response to stimulation (Fig. 5). Similarly the fraction of OT-II cells that produced IL-17 was increased in mice that were immunized in the presence of IL-1 β (Fig. 6). There was also an increase in the frequency of OT-II cells that produced IFN- γ in mice that received IL-1 β but this was less striking than the increase in the frequency of IL-17-producing cells. The increase in the frequency of cytokine producing OT-I and OT-II cells was even more striking in the liver and lung than in spleen and lymph node. Both the proportion of cells producing IFN- γ (OT-I and OT-II) or IL-17 (OT-II) and the amount of cytokine per cell was increased, the latter judged by increase in the MFI of cells stained with fluorescent anticytokine antibodies. Granzyme B levels in OT-I cells were also increased especially in the liver and lung.

In contrast to the IL-1-mediated increase in the frequency of OT-I and OT-II cells in lymphoid organs, the increase in both granzyme B expression and in the proportion of IFN- γ -producing cells among OT-I cells and the augmented IFN- γ production in OT-II cells did not occur if the recipients were IL-1R1^{-/-} mice although the enhancement of the frequency of IL-17-producing cells did not require IL-1R1 expression by non-T cells.

Inclusion of IL-1 in the immunization protocol also increases the cytotoxic activity of primed OT-I T cells. We immunized OT-I transgenic mice with OVA plus LPS with or without IL-1 and transferred increasing number of OT-I cells from the primed donors to naive B6 recipients. We then tested cytotoxic activity of the transferred cells by injecting a mixture of B6 splenocytes labeled with a high concentration of CFSE and loaded with SIINFEKL (the major OVA epitope recognized by the cytotoxic CD8 cells) and of control B6 splenocytes labeled with a low concentration of CFSE. We measured the relative number of CFSE^{high} and CFSE^{low} cells 18 h later in lymph node and spleen cell suspensions. Relative depletion of SIINFEKL-loaded cells in recipients of OT-I cells from the

Figure 3. IL-1 increases the frequency of OT-I and OT-II cells in liver. 10^4 OT-I and OT-II cells were injected into UBC-GFP C57BL/6 mice. Mice were immunized with OVA and LPS with or without IL-1. Seven days after priming, lymphocyte-enriched fractions were isolated from liver by Percoll gradient and cells were analyzed for proportion of OT-I and OT-II cells among the $CD8^+$ and $CD4^+$ populations, respectively.

donors that had been immunized with IL-1 was indicative of their enhanced cytotoxic activity. On a per cell basis, immunization with IL-1 resulted in a >6-fold increase in

the in vivo cytotoxic activity of the primed OT-I cells (Ben-Sasson et al. 2013).

We also immunized normal B6 mice with OVA plus LPS with or without IL-1. The addition of IL-1 increased the frequency of CD8 T cells that bound the SIINFEKL tetramer in both lymph node and spleen, indicating that IL-1 enhances the expansion of antigen-primed normal CD8 T cells as well as transgenic cells. Mice immunized with OVA plus LPS displayed very limited cytotoxic activity for SIINFEKL-sensitized cells as determined by injection of mixture of sensitized and nonsensitized target cells into these animals. In contrast, those that had received IL-1 in the immunization protocol showed striking cytotoxic activity in both lymph nodes and spleen (Ben-Sasson et al. 2013).

Figure 4. The IL-1 induced enhanced expansion of antigen-stimulated OT-I and OT-II cells is less profound in the periphery of IL-1R1^{-/-} recipients. 10^4 CD45.1 OT-I and 10^4 CD45.1 OT-II cells were injected into CD45.2 IL-1R1^{-/-} and wild-type (WT) CD45.2 C57BL/6 mice. Mice were immunized with OVA plus LPS and IL-1. Seven days after priming, cells were analyzed for number of OT-I and OT-II cells in the Percoll gradient-enriched lymphocyte fractions of liver and lung. KO, knockout.

Mice Primed with OVA, LPS, and IL-1 Show Striking Secondary Responses

Mice that had received OT-I and OT-II cells were immunized with OVA and LPS with or without IL-1. Eight weeks later, these mice were challenged subcutaneously with OVA plus LPS, without IL-1. Three days after the boost, there was a larger fraction of OT-I cells among the

Figure 5. IL-1 enhances CD8 T-cell differentiation. 10⁴ OT-I and 10⁴ OT-II cells were injected into UBC-GFP C57BL/6 mice. Mice were immunized with OVA and LPS with or without IL-1. Seven days after priming, cells from the lymph nodes, spleen, liver, and lung were stimulated for 4 h with PMA and ionomycin and the percentage of granzyme B⁺ cells and IFN- γ ⁺ cells among the OT-I cells was determined. Spleen and liver results are illustrated.

Figure 6. IL-1 enhances CD4 T-cell differentiation. 10⁴ OT-I and 10⁴ OT-II cells were injected into UBC-GFP C57BL/6 mice. Mice were immunized with OVA and LPS with or without IL-1. Seven days after priming, cells from the lymph nodes, spleen, liver, and lung were stimulated for 4 h with PMA and ionomycin. The percentage of IL-17⁺ and IFN- γ ⁺ cells among the CD4⁺ GFP⁺ OT-II cells in the various organs was determined. Spleen and lung results are illustrated.

Figure 7. OT-I cells primed in the presence of IL-1 display augmented expansion 8 wk later following a 3 d challenge with OVA + LPS. 10^4 OT-I and 10^4 OT-II cells were injected i.p. into UBC-GFP C57BL/6 mice. Six days later, the mice were immunized with OVA and LPS with or without IL-1. Eight weeks after priming, the mice were boosted with OVA and LPS. Three days later, the percentage of GFP⁺ CD8⁺ OT-I cells among the CD8⁺ cells was determined in the lymphoid organs and in the lymphocyte-enriched Percoll fractions from the liver and lung. Spleen and liver results are illustrated.

CD8 cells in lymph node, spleen, liver and lung in mice that had been originally primed in the presence of IL-1 (Fig. 7). Similarly, the proportion of OT-II cells among the CD4 compartment was increased in the lymph nodes, spleen and especially in the liver and lungs of mice primed with IL-1 (data not shown).

The IL-1-primed memory OT-I cells from each organ showed high frequencies of granzyme B⁺ cells and of OT-I and OT-II cells that produced IFN- γ in response to PMA and ionomycin; memory cells from these organs derived from mice primed without IL-1 showed substantially less granzyme B or IFN- γ . Indeed, in the IL-1-primed groups, the majority of spleen, liver, and lung OT-I cells were granzyme B⁺, and the frequency of IFN- γ -producing cells in these organs was $\sim 40\%$. Thus, the striking phenotypic properties of OT-I cells observed 7 d after priming with IL-1 were also observed when these mice were boosted 8 wk later, even though IL-1 was not administered in the booster immunization.

Gene Expression in OT-II Cells Undergoing IL-1-Mediated Expansion

WT OT-II and IL-1R1^{-/-} OT-II cells were transferred to WT recipients that were immunized with OVA, LPS and IL-1. Three days later, the OT-II cells in lymph nodes and the spleens were purified by cell sorting and gene

expression analysis performed on Agilent and Illumina platforms.

Employing Ingenuity Analysis, the comparison of WT and IL-1R1^{-/-} T cells showed that IL-1 induced a pattern of gene expression consistent with enhancement of cell cycle, DNA replication, recombination and repair, cellular growth and proliferation, and cell survival pathways. These results are consistent with our prior analysis of T-cell proliferation and survival in response to in vivo administration of IL-1.

In addition, expression of genes included within canonical pathways regulating metabolism and energy were significantly different between the IL-1R1^{+/+} and IL-1R1^{-/-} OT-II cells.

IL-1 Enhances Protectivity of Weak or Ineffective Vaccines

We wished to determine whether the striking IL-1-mediated enhancement in both CD4 and CD8 T-cell expansion and the accompanying increase in effector phenotype would allow greater efficacy of weak vaccines if IL-1 was included in the vaccination protocol. We chose five model systems for analysis. Heat-killed *Listeria monocytogenes* as a vaccine for challenge with live *L. monocytogenes*, glycoprotein D (gD2) of herpes simplex virus (HSV) as a vaccine for HSV, heat-killed *Blas-tomyces dermatitidis* as a vaccine for challenge with live

B. dermatitidis, HIV gp160IIIB peptide as a vaccine for HIV gp160IIIB-expressing vaccinia virus and HPV E749-57 peptide as an enhancer of immune response against established transplanted HPV-transformed tumor.

In each instance, the inclusion of IL-1 in the priming protocol increased the protection offered by immunization. The results for the *L. monocytogenes*, HIV gp160IIIB-expressing vaccinia, transplanted HPV-transformed tumor and *B. dermatitidis* have been published (Ben-Sasson et al. 2013; Wüthrich et al. 2013). Here we show enhancement of protection against HSV challenge by inclusion of IL-1 in the gD2-priming protocol. Immunization with the gD2 subunit HSV vaccine did not provide effective protection against challenge with HSV 1 mo later; 9/10 challenged mice died by day 14. However, administration of IL-1 with the gD2 vaccine resulted in significant protection, with 6/10 mice surviving the lethal HSV challenge (Fig. 8).

DISCUSSION

Here we have both reviewed previous work and presented new results demonstrating that IL-1 β strikingly enhances both CD4 and CD8 antigen-specific T-cell responses. We have studied the effect of adding IL-1 to an immunization regimen involving both antigen and LPS; in earlier work we showed that IL-1 β enhances responses to antigen-specific CD4 T cells even in the absence of an exogenous adjuvant. In contrast to most exogenous adjuvants, the expansion of antigen-specific CD4 T cells at the site of priming reflects the direct action of IL-1 on responding T cells. Indeed, in previous experiments we showed that in IL-1R1^{-/-} mice that received a mixture of wild-type and IL-1R1^{-/-} antigen-specific CD4 T cells, only the wild-type cells responded, arguing strongly that the expansion response at the site of priming is cell autonomous (Ben-

Sasson et al. 2009). We previously reported that the IL-1-mediated expansion of responding CD4 T cells could be accounted for mainly by increased cell survival although a modest component of greater proliferation was also observed (Ben-Sasson et al. 2009). Consistent with this result, gene expression profiling revealed that IL-1 activated both cell survival pathways and pathways associated with cell division as well as enhanced metabolic activity. IL-1 β is known to activate NF- κ B (Bowie and O'Neill 2000b) and MAP kinases (O'Neill 2002) and has recently been reported to activate the mTOR pathway (Chang et al. 2013). The relative contribution of each of these pathways to the IL-1 β enhancement of T-cell expansion and differentiation needs to be established.

While some of IL-1 β 's effects on T-cell differentiation require expression of IL-1R1 only on the responding T cells, others, including expression of granzyme B, capacity to produce IFN- γ and cytotoxic activity of CD8 cells, also require that a non-T cell expresses IL-1R1. An obvious possibility for these activities is the action of IL-1 β on dendritic cells; this needs to be determined.

IL-1 β strikingly enhances the frequency of both antigen-specific CD4 and CD8 T cells that enter the liver and lung, functions of great importance in protective responses to tissue-localized pathogens. Here too, IL-1R1-expression by cells other than the responding T cells is essential for enhanced frequency of antigen-responsive cells in these tissues. Although IL-1 β has been reported to regulate adhesion and/or transmigration of lymphocytes into various tissues by controlling chemokine production (McCandless et al. 2009) and possibly adhesion molecule expression (Mohamadzaheh et al. 1998), the target cell of IL-1 β needs to be established as does the mechanism through which this accumulation occurs, be it entry into, retention in, or proliferation in the peripheral tissue.

As we have indicated in the Introduction and illustrated in the Results section, IL-1 β enhances responses that appear to be both necessary and sufficient for robust protective immunity—namely, marked expansion of antigen-specific CD4 and CD8 T cells, differentiation of those cells to effector cells, accumulation of effector cells in peripheral organs, and maintenance of memory. In five distinct vaccine models, we have observed that inclusion of IL-1 β in the priming protocol will strikingly enhance the protective value of the vaccine, even in instances when the vaccine alone has little or no efficacy. This implies that IL-1 β or a congener could be effective in inducing protective immunity in response to current vaccines that have relatively limited efficacy. If the generalized proinflammatory functions of IL-1 β could be minimized while retaining its capacity to enhance immune responses, IL-1 β could be considered in vaccination protocols.

ACKNOWLEDGMENTS

The research on which this work is based was supported by the National Institute of Allergy and Infectious Diseases Division of Intramural Research through Projects Z01-AI000493-27 and Z01-AI000926-13. We thank Jane Hu-Li, Stephane Caucheteux, and Michelle Crank

Figure 8. IL-1 enhances the efficacy of herpes simplex virus 2 (HSV-2) glycoprotein D (gD2) subunit vaccine against lethal intravaginal challenge with wild-type HSV-2. Six-week-old female C57B/6 mice were vaccinated i.m. with HSV-2 gD2 subunit vaccine consisting of 3 μ g of recombinant gD2 protein, 75 μ L of alum, and 7.5 μ g of MPL with or without IL-1. IL-1 (2 μ g/mouse) was given s.c. for 5 consecutive days beginning on the day of the vaccination. Thirty days after vaccination, all mice were treated with medroxyprogesterone acetate (2 mg/mouse s.c.) to enhance their susceptibility to intravaginal HSV-2 infection. Five days later mice were challenged with 6.5×10^5 pfu of HSV-2 strain 333 intravaginally.

for their contributions to the study of IL-1 β effects on CD4 and CD8 T cells, Ran Nir-Paz, Alison Hogg, Jay Berzofsky, Marcel Wüthrich, and Bruce Klein for their collaboration in the study of IL-1 enhancement of vaccine effects, Tim Myers for his help with the interpretation of gene expression data, and Paul Wingfield for his generous gifts of IL-1 β and advice on use of the cytokine.

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Cold Spring Harbor Symposia on Quantitative Biology

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Cold Spring Harb Symp Quant Biol 2013 78: 117-124 originally published online October 3, 2013
Access the most recent version at doi:[10.1101/sqb.2013.78.021246](https://doi.org/10.1101/sqb.2013.78.021246)

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