Review

The Common γc-Cytokines and Transplantation Tolerance

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Transplant rejection, like tolerance, is a T cell-dependent event. There is compelling evidence to suggest that induction of transplant tolerance is an actively learned process in which T cells need to engage with the alloantigens in order to learn to tolerate the allograft. A family of cytokines whose receptors use the same IL-2 receptor γc chain (also called the common γc) plays an important role in regulating multiple aspects of the allograft response (i.e. rejection vs. tolerance). It is undeniable that γc cytokines can drive clonal expansion and effector maturation of alloreactive T cells, and therefore, targeting such cytokines or their receptor components remains an attractive way of blocking transplant rejection. However, we just started to appreciate that γc cytokines also regulate the acquisition of transplant tolerance via programming activated T cells for apoptotic cell death and via guiding the evolution of regulatory T cells. Thus, understanding precisely the role of γc cytokines in regulating T cell homeostasis and T cell regulation is critically important in the induction of transplant tolerance. *Cellular & Molecular Immunology*. 2004;1(3):167-172.

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A family of structurally related cytokines (i.e. IL-2, IL-4, IL-7, IL-9, IL-15, IL-21) whose receptors share the identical IL-2 receptor γc chain is often called the γc-dependent cytokines (Figure 1). A key feature of γc-cytokines is that all of them possess potent T cell mitotic activities capable of driving rapid T cell proliferation and effector differentiation (1, 2). It is now clear that γc-cytokines regulate several aspects of immune activation during the allograft response. They play an important role in supporting survival, proliferation and effector function of activated T cells. Thus, blocking such cytokines often attracts considerable attention in attempting to prevent transplant rejection. However, certain γc-dependent cytokines also play an essential role in programming activated T cells for activation induced cell death (AICD), a key process involved in T cell homeostasis and peripheral tolerance (3). More importantly, there is compelling evidence to suggest that some γc-cytokines are probably indispensable in the development of regulatory T cells that may prove to be critical to long-term maintenance of a tolerant state (4). Hence, the fate of an allograft (rejection vs. tolerance) may be dependent on the balanced acts of such cytokines in affecting the life and death of activated T cells as well as in guiding the evolution of regulatory T cells. This article will review our recent understanding of γc-cytokines in the regulation of T cell homeostasis with special emphasis on transplantation.

Role of γc-cytokines in T cell activation

Upon engagement of the T cell receptor (TCR) along with certain costimulatory receptors, T cells often acquire exquisite sensitivity to respond to γc-dependent cytokines. In fact, once T cells pass the stage of antigen specificity during the activation process, the fate of such activated T cells as to become armed effector cells, to commit to apoptotic cell death, or to evolve as immune regulatory T cells is regulated, to a large extent, by the γc-cytokines (5). Indeed, when activated T cells are deprived of certain γc-cytokines at a critical stage of cell activation, the immune activation is often aborted or the T cell activation program altered (6).

Despite tremendous redundancy among the γc-cytokines in stimulating T cell proliferation, not all γc-cytokines function in the same way. In the past few years, it has been appreciated that individual γc-cytokines exhibit certain overlaps but also distinct functional characteristics. For example, IL-2 as a T cell growth factor *in vitro* is undeniable, while IL-2 also plays an indispensable role in priming activated T cells for apoptotic cell death, a feature that is not readily shared by other γc-cytokines (7). IL-4 is instrumental in the development of Th2 immunity (8). IL-7 is absolutely required for intra-thymic T cell development (9). In immune competent hosts, IL-7 appears to be

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Abbreviations: AICD, activation induced cell death; FLIP, Flice inhibitory protein; NKT cells, natural killer T cells; MHC, major histocompatibility complex; TCR, T cell receptor.

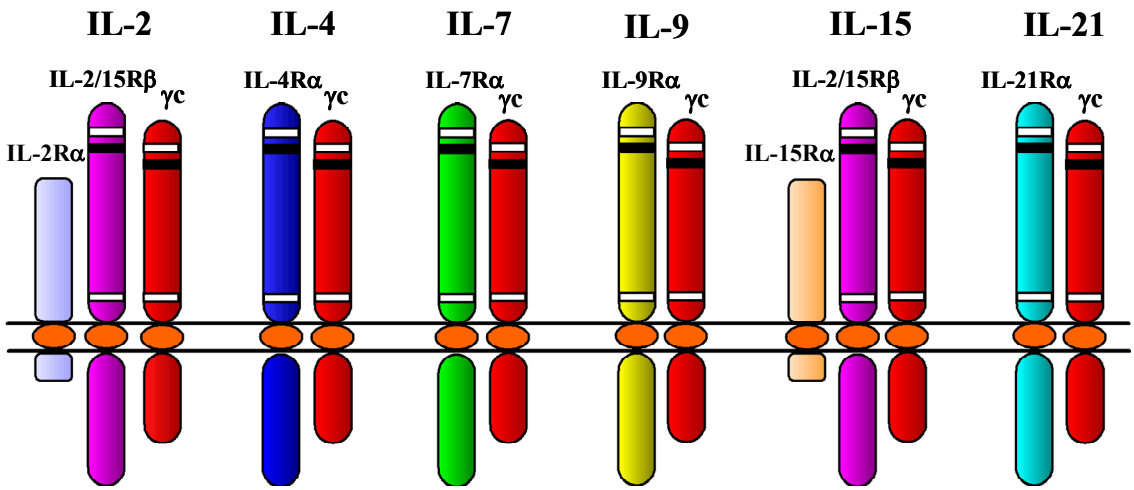

Figure 1. The common γc as a shared receptor component. The receptors for IL-2 and IL-15 consist of a private α chain but share the IL-2Rβ chain and the γc chain. The receptors for IL-4, IL-7, IL-9, and IL-21 are composed of a distinct α chain, which defines the cytokine specificity and the common γc chain.

important in supporting the survival of naïve T cells in the periphery under physiologic conditions (10). The role of IL-9 has been rather mysterious until the generation of IL-9 deficient mice. It is now clear that IL-9 is a key growth factor for mast cells, mucosal goblet cells and certain transformed T cells, but IL-9 has a limited role in the proliferation of primary T cells (11). IL-15 is a recently discovered cytokine that shares many features with IL-2 (12). In contrast to IL-2, however, IL-15 acts as a survival factor for a variety of cell types and plays an essential role in supporting $CD8^+$ T cells, especially the memory $CD8^+$ cells (13, 14). IL-15 is also required for development and survival of NK cells, NKT cells, and intra-epithelial lymphocytes. IL-21 is a new member in the γc family and its function is just starting to be unraveled. In certain models, IL-21 can stimulate the cytolytic activity of $CD8^+$ T cells and NK cells, but IL-21 by itself does not support the survival of NK cells. Interestingly, IL-21 can block IL-15 stimulated NK cell expansion (15). Thus, IL-21 may be at the interface between innate immunity and acquired immunity. However, a recent report suggested that IL-21 is a Th2 cytokine and capable of inhibiting IFN-γ production by Th1 cells (16). In this regard, the precise relationship between IL-21 and IL-4 remains completely unknown. Clearly, a balanced act of γc-cytokines is undoubtedly important in shaping up the nature of the T cell response.

It should be emphasized that not all γc-dependent cytokines are produced by the same kind of cells. IL-2 is produced primarily by activated T cells, especially $CD4^+$ T cells and production of IL-2 is tightly regulated at the transcriptional level. Several key costimulatory molecules including CD28 play an important role in promoting IL-2 production. IL-4 is mainly from Th2 cells, NKT cells, and some unconventional cell types such as eosinophils. Interestingly, transcriptional activation of the IL-4 gene requires cell cycle progression, suggesting that cell cycle regulators may contribute to the IL-4 gene expression (17). IL-21 is also a T cell product, and the precise mechanism regulating IL-21 expression remains largely unknown. On the other hand, IL-7 and IL-15 are not produced by T cells. Epithelial cells, stromal cells, and to a certain degree the platelets, are the major source of IL-7. Similarly, a wide variety of cell types including macrophages, dentritic cells, endothelial cells, myocytes, keratinocytes, and even the neurons can produce large amount of IL-15 (18). Furthermore, production of IL-15 is regulated not only at the transcriptional level but also at the post-transcriptional level, and a significant proportion of IL-15 is membrane bound rather than secreted (18). Thus, the *in vivo* availability and accessibility of IL-7 and IL-15 to T cells are likely to be different as compared to the T cell derived cytokines. Moreover, the non-T cell origin of IL-7 and IL-15 also suggests that the *in vivo* availability of IL-7 and IL-15, as opposed to IL-2 and IL-4, is not strictly dependent on T cell activation per se. Therefore, it is likely that activation of T cells can affect the nature of the cytokine milieu and the nature of the T cell response can be influenced by distinct γc-cytokines.

It is quite interesting that the cell surface receptors for the γc-cytokines are polymeric structures (Figure 1). The receptors for IL-2 and IL-15 consist of a private α chain that defines the binding specificity for IL-2 or IL-15 and the shared IL-2Rβ chain and γc chain. The receptors for IL-4, IL-7, IL-9, IL-21 are composed of a distinct α chain and the γc chain (1). Different receptor components can be expressed individually on T cells but they have to associate with each other in order to function as a high affinity receptor complex. Thus, differential receptor configurations on the surface of activated T cells certainly affect their responsiveness to different cytokines. We have recently shown using an *in vivo* cell division model that during the initial 4 to 5 cell divisions, activated T cells express the IL-15Rα chain but not the IL-2Rα chain (19). As the shared β chain and the γc chain are constitutively expressed, T cells at the early activation stage are primarily IL-15, but not IL-2, responsive. However, IL-2 appears to be important

in the later stage of T cell response as the IL-2Rα chain is highly expressed after 5 cell divisions (19). The precise mechanisms that control such differential configuration of cytokine receptors on actively cycling T cells are completely unknown. Nonetheless, the T cell activation status, availability of certain cytokine *in situ*, accessibility of receptor subunits, and possibly the nature of costimulatory signals may all contribute to the selective responsiveness of activated T cells to different γc-cytokines.

The γc-cytokines in life and death of effector T cells

The ability of T cells to be able to proliferate and rapidly expand after antigenic encounter is truly remarkable. In certain models, antigen specific T cell clones can expand over 100 times of their original size within just a matter of days following antigen exposure (5). However, overwhelming majority of such expanded T cells (>90%) have to die via a process called apoptosis when the offending antigen is cleared, as the immune system simply does not have the space to accommodate all the activated T cells from every immune response. T cell apoptosis also helps the immune system to reset its balance, a process called T cell homeostasis. Failure to control apoptosis of activated T cells is certainly devastating to the hosts. It is clear now that certain TCGFs are fundamentally important in regulating multiple aspects of this process.

A paramount example in this regard is the striking phenotype of IL-2 knockout mice. Despite the mounting evidence of IL-2 as a key growth factors *in vitro*, mice deficient for IL-2 are not immunodeficient but rather develop a profound lymphoproliferative syndrome characterized by continued expansion of activated T cells in the periphery (20). Similar phenotype is present in mice deficient for the IL-2Rα chain or the IL-2Rβ chain. Thus, IL-2 appears to perform a dual role in the T cell response, a growth factor for T cell proliferation and also a death factor for activated T cells. It remains unclear how IL-2 does this opposing function. IL-2 by itself is not directly cytotoxic, but it can modify the survival and/or the death program of activated T cells, and cell cycle transition seems to be required in this regard. There are two general pathways by which T cell apoptosis can be initiated, i.e. engagement of cell surface death receptors (e.g. Fas) or deprivation of survival signals to activated T cells (e.g. down-regulation of Bcl-2 family proteins) (21). IL-2 seems to affect both of these apoptotic pathways. It has been shown that IL-2 can transcriptionally shutdown the expression of FLIP, an inhibitory protein downstream of Fas (22), allowing Fas to recruit and activate caspases to execute the apoptotic process (23). We have recently shown that IL-2 can also bring down the surface expression of γc, and therefore, rendering cells susceptible to apoptosis by decreasing Bcl-2 expression (19). Interestingly, γc down-regulation occurs only after certain numbers of cell divisions *in vivo* and also requires functional IL-2 (19).

Whether cytokines other than IL-2 (i.e. IL-4, IL-7, IL-9, IL-15, IL-21) can program activated T cells for apoptosis remains enigmatic. Under certain conditions, high levels of IL-4 and IL-7 have been shown to induce apoptotic death of activated T cells *in vitro* (24), however, their roles *in vivo* are less clear. IL-4 knockout mice do not have apparent defects in apoptosis, suggesting that IL-4 has a minimal role in priming T cells to undergo activation induced cell death *in vivo* (8). Although IL-7, like other γc-cytokines, stimulates vigorous proliferation of activated T cells, IL-7 has been shown to protect lymphoid cells from undergoing apoptosis (25). Interestingly, transgenic expression of IL-9 in mice induces formation of lymphomas (26), suggesting that IL-9 has intrinsic features of promoting tumogenesis rather than priming for apoptosis. IL-15 binds to a trimeric cell surface receptor that shares both the IL-2Rβ chain and the γc chain. IL-15, like IL-2, is remarkably potent in supporting T cell proliferation *in vitro*. In contrast to IL-2, however, IL-15 appears to prevent apoptosis and promote cell survival (27). Indeed, mice deficient for IL-15 or IL-15Rα chain have a lymphopenic phenotype (28, 29), which is diametrically opposed to that of the IL-2 deficient mice. On the other hand, overexpression of IL-15 as a transgene in mice leads to the eventual development of lymphocytic leukemia (30), further supporting the claim that IL-15 is an important survival factor. The precise function of IL-21 *in vivo* and its relationship with other γc-cytokines remain to be clearly defined. However, certain evidence suggests that IL-21 can support effector function of T cells and NK cells but does not support the survival of NK cells (15), and how such different functions are accomplished by IL-21 is entirely unknown.

Clearly, regulation of T cell survival and T cell apoptosis is a delicate teamwork and a balanced act of all γc-dependent cytokines is of central importance. Thus, abnormality of either one of them can have a profound impact on the homeostasis of the immune system.

Role of γc-cytokines in regulatory T cell function

Regulatory T cells, particularly the $CD4^+CD25^+$ regulatory T cells, have received tremendous attention recently. In the transplantation setting, generation of regulatory T cells that can suppress the alloreactive T cells escaping the initial tolerizing therapy is undoubtedly important in the maintenance of a tolerant state over time. In fact, active immune suppressive mechanisms involved in allograft tolerance have been repeatedly demonstrated in several transplant models (31). However, the identity of suppressor cells, and more importantly, the signals and signs required for their development and function have defied our full understanding. As T cells involved in the allograft rejection are extremely diverse, it is likely that the regulatory cells that actively suppress the alloimmunity are also heterogeneous.

As mentioned above, the cell type that received most attention now is the $CD4^+CD25^+$ regulatory T cells. $CD4^+$ $CD25^+$ cells are originated in the thymus and exported to the periphery where they function as potent suppressor cells (32). $CD4^+CD25^+$ cells are clearly important in controling the development of autoimmune diseases and in certain models maintaining transplant tolerance (33,34). Although the precise mechanisms concerning their deve-

lopment and their acquisition of antigen specificity in mediating suppression are poorly characterized, IL-2 seems to be essential for the functional integrity of $CD4^+CD25^+$ T cells. IL-2 plays an important role in development, survival and expansion of such cell type, as $CD4^+CD25^+$ T cells are defective in IL-2 deficient and IL-2Rα deficient mice (35).

In certain transplant models, the tolerant status can be adoptively transferred by T cells to a new cohort of naïve animals, a phenomenon called "infectious allograft tolerance" (36). Adoptive transferring of the tolerant status is critically dependent on $CD4^+$ T cells. Several important points should be emphasized in this model. First, suppressor T cells developed in the primary tolerant hosts are extremely effective in suppressing the alloreactive effector T cells in the secondary hosts. Second, such suppressor T cells can convent naïve T cells into suppressor T cells in the secondary hosts. Third, the suppressor mechanism once established is a robust and self-perpetuating process. In some models, suppression is probably mediated by IL-4 dependent immune deviation. For example, the ability of tolerant $CD4^+$ T cells to transfer allograft tolerance to secondary hosts can be blocked by neutralizing IL-4 during the induction of tolerance in the primary recipients (37), suggesting a critical role of IL-4 in regulating this process. Recently, IL-15 has been implicated as a key cytokine in survival and expansion of memory T cells (38). Whether IL-15 can also stimulate the development of T cells with regulatory properties is unknown. IL-15 is clearly important in development and probably also in survival of NKT cells that are capable of suppressing certain autoimmune diseases (39, 40). However, their role in transplant tolerance remains to be determined.

Role of γc-cytokines in allograft rejection

The role of IL-2 in acute allograft rejection, a process often associated with a Th1 type immune activation, is compelling. However, IL-2 deficient mice remain capable of vigorously rejecting the MHC mismatched allografts with a kinetics that is comparable to the wild type controls. IL-4 deficient mice also readily reject islet and cardiac allografts. Moreover, mice deficient for both IL-2 and IL-4, two classical T cell derived cytokines, also vigorously reject islet allografts (41). Rejection in this model is clearly a T cell dependent process as rejection of the islet allografts in IL-2/IL-4 double knockout mice showed a classical mononuclear infiltrate. Rejection in this model was also associated with intra-graft expression of CTL gene transcripts, and graft survival can be prolonged by targeting T cells using the anti-CD3 mAb. IL-7 and IL-15, the non-T cell derived cytokines, are highly expressed during IL-2/IL-4 independent allograft rejection (41). The critical role of IL-7 and IL-15 in supporting the IL-2/IL-4 independent rejection is further highlighted by the finding that treatment of IL-2/IL-4 double knockout mice with anti-γc mAbs can markedly prolong the allograft survival. In a minor antigen mismatched heart transplant model, blocking the IL-15/IL-15R using the soluble IL-15Rα chain induced prolonged allograft survival, albeit this protocol had minimal effect in prolonging fully MHC mismatched allografts (42). Interestingly, despite expression of other γc-cytokines in rejecting allografts, IL-9 gene transcripts were conspicuously absent. These findings suggest that regulation of IL-9 is distinct from that of IL-2, IL-4, IL-7 and IL-15, and that IL-9 is unlikely to play a key role in acute allograft rejection.

Similar to our findings in the mouse, we and others have routinely found IL-7 and IL-15, but not IL-9, gene transcripts in rejecting renal allografts from patients under conventional immunosuppression (43). As IL-7 and IL-15 expression is often resistant to cyclosporin A, it is likely that IL-7 and IL-15 may play an important role in chronic allograft rejection in humans under conventional immunosuppression. Clearly, the γc-cytokines are remarkably redundant in supporting T cell activation and acute allograft rejection, and absence of either one of them is unlikely to have a significant impact on the rejection response, especially across the full MHC barriers.

Role of γc-cytokines in allograft tolerance

In an effort to understand the role of γc-dependent cytokines in the induction of transplant tolerance, we and others have found that it is extremely difficult, if not impossible, to tolerize IL-2 knockout mice using tolerizing protocols that are not inherently lymphoablative. In an islet transplant model, treatment of IL-2 knockout mice with rapamycin, anti-CD3, or anti-γc mAbs failed to induce stable engraftment and all islet allograft were eventually rejected. In contrast, rapamycin treated wild type control mice experienced long-term islet allograft survival (44). Similar finding was reported in a cardiac transplant model in which costimulatory blockade uniformly created a long term cardiac allograft survival in wild type control mice but it failed to do so in IL-2 knockout mice (45). Hence, IL-2 is not required for rejection but seems to be indispensable for tolerance induction.

A defect in apoptotic death of activated T cells seems to contribute to the failure of tolerance induction in the IL-2 deficient mice. This claim is strengthened by the finding that mice with transgenic expression of Bcl-xL, a potent anti-apoptotic molecule, in the T cell lineage is also resistant to the induction allograft tolerance using the costimulatory blockade protocol (44). In fact, T cells from the Bcl-xL transgenic mice have incredible longevity both *in vitro* and *in vivo* regardless of their activation status. As a consequence of such survival advantage, treatment of Bcl-xL transgenic mice with donor specific transfusion plus CTLA-4Ig or anti-CD40L mAb failed to prevent cardiac allograft rejection while this protocol consistently produced uniform allograft survival in the wild type control mice (44). We also established the same principle in conventional mice. Treatment with costimulatory blockade (i.e. CTLA-4Ig and anti-CD40L) plus cyclosporine, a protocol that completely prevented T cell activation and T cell apoptosis, also precluded the induction of skin allograft tolerance whereas promoting T cell apoptosis by the provision of rapamycin to the costimulatory blockade protocol facilitated tolerance induction (46). Despite the close relationship between IL-2 and the functional integrity of the Fas triggered apoptotic pathway, allograft tolerance can be readily induced in Fas deficient mice (47),

suggesting that an IL-2 driven apoptotic process that is independent of Fas is critically important in these models, although the precise mechanisms remain to be clearly defined.

The role of other cytokines in the induction of allograft tolerance is less well studied. Allograft tolerance can be induced in the absence of IL-4. However, using certain immunosuppressive protocols, especially those that can directly kill host lymphocytes, induction of allograft tolerance appears to be difficult in IL-4 deficient mice (48), suggesting that in certain but not all models IL-4 may be required for the induction transplant tolerance. As IL-4 is instrumental in the development of Th2 cells and a Th2 environment has been suggested to be permissive for tolerance induction, the requirement of IL-4 may be related to the activation of Th2-like immune regulatory network that facilitate tolerance induction. Indeed, in a cardiac transplant model, neutralizing IL-4 at the time of transplantation blocked the adoptive transfer of tolerance to the secondary hosts, albeit stable cardiac allograft survival in the primary hosts was not affected (49). Similar finding was reported in other transplant models (4). In an islet transplant model, blocking the common γc, the shared receptor element by all known γc-cytokines, induced precipitous T cell apoptosis and stable allograft tolerance (50). However, the individual role of IL-7, IL-15, and IL-21 in transplant tolerance is still unknown, and further research in this area is warranted in the future.

Concluding remarks

Clearly, the impact of γc-cytokines on T cell activation, T cell apoptosis, and the evolution of regulatory T cells is far more complex than initially anticipated. As transplant rejection entails the direct recognition of foreign MHC molecules and the activation of an unusually large alloreactive clonal size, we believe that an apoptotic process initiated by some γc-cytokines during T cell activation is critically important in the induction peripheral allograft tolerance with regimens that do not directly kill host lymphocytes. The initial apoptotic process may also promote or foster selective survival of regulatory T cells that maintain the tolerant status over time. Clearly, a balanced act of γc-cytokines is critically important in this regard. A detailed understanding of γc-cytokines in the allograft response will undoubtedly lead to the design of more effective strategies to induce long-term engraftment in the clinic.

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