role in activating T cells in allergen-specific T cell-mediated immune responses.

The pathologic roles of these cytokines and the functional interrelationship among these cytokines in the development of arthritis, aortitis, and dermatitis that develop in IL-1Ra$^{-/-}$ mice, however, remain to be elucidated. In this paper, we will describe the roles for TNFα and IL-17 in the development of diseases resulting from excess IL-1 signaling.

8.2 The Roles of TNFα and IL-17 in the Development of Arthritis

8.2.1 Development of Autoimmune Arthritis in IL-1Ra$^{-/-}$ Mice

IL-1Ra$^{-/-}$ mice on the BALB/c background developed arthritis spontaneously; arthritis began to develop at 5 weeks of age and almost all of the animals suffered from arthritis at 12 weeks of age (Horai et al. 2000). The incidence of arthritis in IL-1Ra$^{-/-}$ mice differed among different genetic backgrounds; the incidence was high on the BALB/c background, but low on the C57BL/6 background, suggesting involvement of BALB/c-specific host genes. The histopathology of the lesions demonstrated a marked synovial and periarticular inflammation with articular erosion caused by invasion of granulation tissues, closely resembling the phenotype of RA in humans (Fig. 1). Osteoclast activation was obvious at the pannus, while inflammatory cell infiltration, consisting mostly of neutrophils, and fibrin clots were detectable in the synovial spaces.

Both total immunoglobulin levels and the levels of autoantibodies specific for immunoglobulin, type II collagen, and dsDNA were elevated in IL-1Ra$^{-/-}$ mice (Horai et al. 2000). The development of arthritis was completely suppressed in *scid/scid*-IL-1Ra$^{-/-}$ mice and adoptive transfer of IL-1Ra$^{-/-}$ T cells induced arthritis in *nu/nu* mice, suggesting a critical role for T cells in the pathogenesis of arthritis in this animal model (Horai et al. 2004). Arthritogenic activated and/or memory T cells were generated in IL-1Ra$^{-/-}$ mice, because T cells from arthritic IL-1Ra$^{-/-}$ mice could transfer disease more efficiently than those from nonarthritic mice. Since IL-1Ra mRNA expression was observed even in unstimulated T cells at low levels and the expression was enhanced

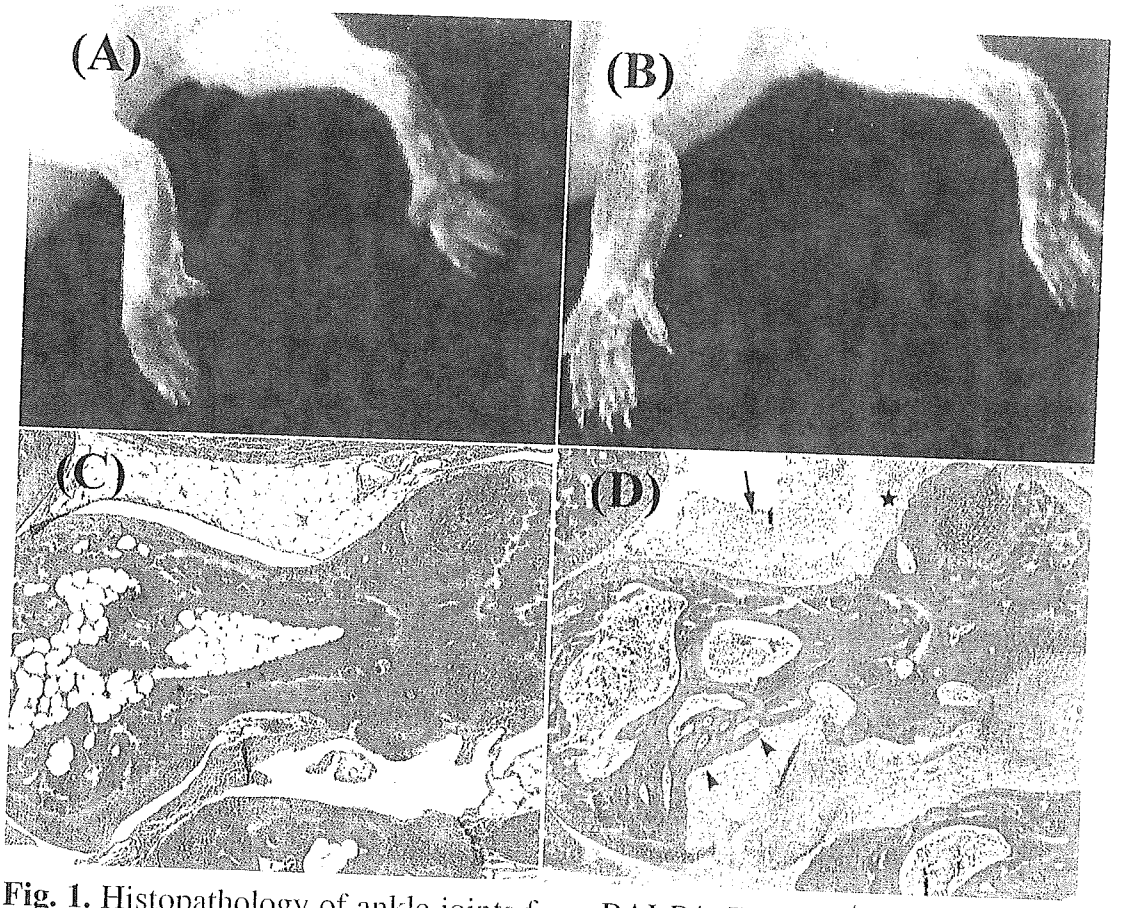

Fig. 1. Histopathology of ankle joints from BALB/c-IL-1Ra$^{-/-}$ mice. The ankles of a normal IL-1Ra$^{+/+}$ mouse (**A**) and an affected IL-1Ra$^{-/-}$ mouse (**B**) were examined at 16 weeks of age. Swelling and redness of the joints were observed in the IL-1Ra$^{-/-}$ mouse. Microscopic observation of the joints of IL-1Ra$^{+/+}$ (**C**) and IL-1Ra$^{-/-}$ (**D**) mice demonstrated the erosive destruction of bone in the IL-1Ra$^{-/-}$ mouse (*arrowheads*). The infiltration of inflammatory cells (*arrows*) and the proliferation of the synovial membrane lining cells (*asterisk*) were remarkable

in activated T cells, these data suggest that, although IL-1Ra is produced by cells of various types including monocytes and macrophages in the synovial lining layer, T cell-derived IL-1Ra likely regulates T cell activity in an autocrine manner.

We have previously shown that antigen-presenting cell (APC)-derived IL-1 can promote T cell activation through the induction of CD40L and OX40 on T cells, suggesting that IL-1 is an important regulator of acquired immune responses (Nakae et al. 2001b). In support of this notion, antibody production against sheep red blood cells increased in

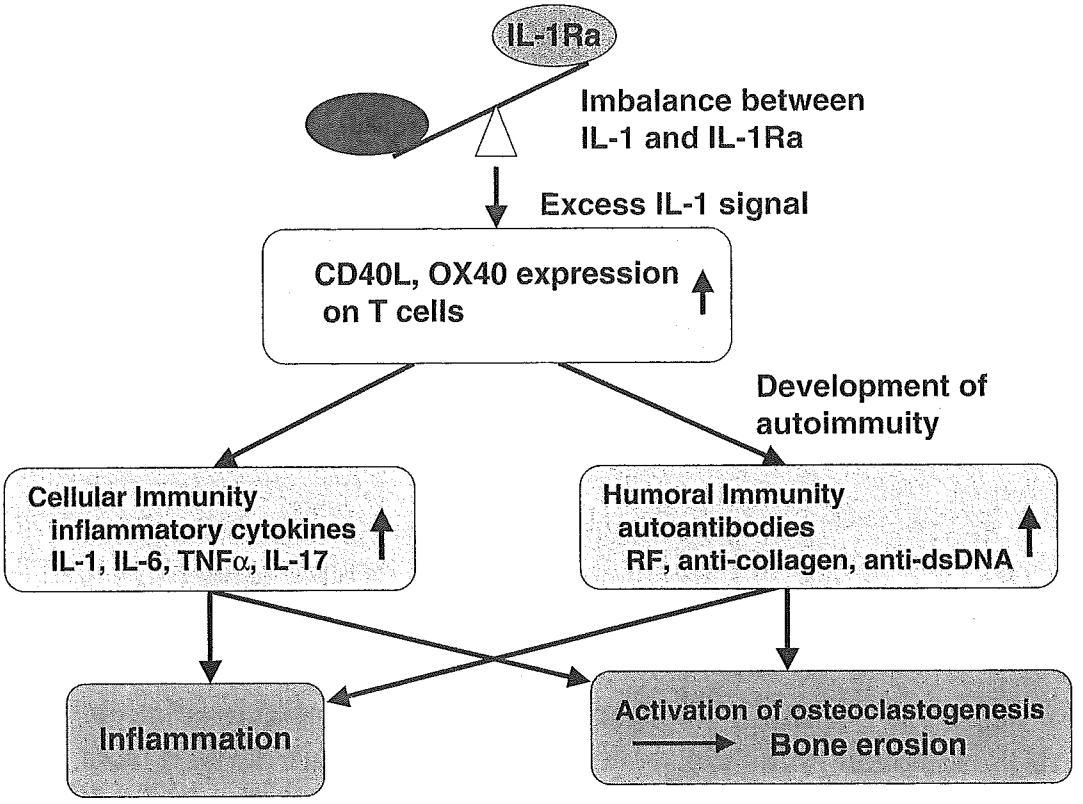

Fig. 2. Excess IL-1 signaling causes autoimmune arthritis

IL-1Ra$^{-/-}$ mice and decreased in IL-1$^{-/-}$ mice (Nakae et al. 2001a). Thus, it is suggested that, in the absence of IL-1Ra, even physiological levels of IL-1, which is constitutively expressed in the joints, can activate naive T cells excessively, resulting in the development of autoimmunity. These observations indicate that the balance between IL-1 and IL-1Ra is critical for homeostasis of the immune system (Fig. 2).

8.2.2 The Role of TNFα in the Development of Arthritis

The expression of numerous inflammatory cytokines, including TNFα and IL-17, was augmented in the joints of IL-1Ra$^{-/-}$ mice. To elucidate the roles of these cytokines in arthritis development, we examined the effect of cytokine deficiency on disease initiation and progression. We determined that the development of arthritis was markedly suppressed in TNFα$^{-/-}$ mice, indicating the crucial role for TNFα in pathogenesis (Horai et al. 2004). A dominant role for TNFα in the development of

RA has been demonstrated by recent clinical trials using therapeutic anti-TNFα antibody (Feldmann and Maini 2001). Studies in the type II collagen-induced arthritis (CIA) mouse model also support this notion (Thorbecke et al. 1992; Joosten et al. 1999; Feldmann and Maini 2001).

While bone marrow (BM) cell transplantation from TNFα$^{+/+}$-IL-1Ra$^{-/-}$ mice into γ-ray-irradiated wild-type (WT) recipient mice induced arthritis, TNFα$^{-/-}$-IL-1Ra$^{-/-}$ BM cells could not induce arthritis. These results indicate that BM-derived cells are responsible for the production of TNFα (Horai et al. 2004). It is interesting, however, that TNFα$^{-/-}$-IL-1Ra$^{-/-}$ BM cells could induce arthritis when inoculated into IL-1Ra$^{-/-}$, but not WT recipient mice. Since TNFα expression is augmented in the joints of IL-1Ra$^{-/-}$ mice, this TNFα may compensate for the deficiency in the BM-derived cells. T cells are sensitive to irradiation, while synovial lining cells are relatively resistant to irradiation. Some of the synovial lining cells, such as type A cells, are derived from the BM origin and are eventually replaced by donor cells after BM cell transplantation. In recipient IL-1Ra$^{-/-}$ mice, TNFα is likely produced by these synovial lining cells, which may donate the arthritogenic milieu observed in IL-1Ra$^{-/-}$ mice in BM cell transfer experiments.

Furthermore, we found that the transfer of TNFα$^{-/-}$-IL-1Ra$^{-/-}$ T cells into *scid/scid* mice did not promote the development of arthritis as robustly as TNFα$^{+/+}$-IL-1Ra$^{-/-}$ T cells, suggesting that T cells are not efficiently sensitized in TNFα$^{-/-}$ mice (Table 1). Thus, these results

Table 1. Inefficiency of the development of arthritis in *scid/scid* mice transferred with T cells from TNFα$^{-/-}$-IL-1Ra$^{-/-}$ mice

Donor	Arthritis	
	Incidence	Score
TNFα$^{+/+}$-IL-1Ra$^{-/-}$	4/5	5.0
TNFα$^{-/-}$-IL-1Ra$^{-/-}$	1/11*	7.5
TNFα$^{+/+}$-IL-1Ra$^{+/+}$	0/5**	0.0

Splenic CD4^{+}T cells (5×10^7) were transferred into BALB.B-*scid/scid* mice, and the development of arthritis was inspected after 12 weeks

* $p < 0.05$ vs TNFα$^{+/+}$-IL-1Ra$^{-/-}$ mice by χ^2 test

** $p < 0.01$ vs TNFα$^{+/+}$-IL-1Ra$^{-/-}$ mice by χ^2 test

suggest that TNFα derived from both T cells and synovial lining cells is involved in the development of arthritis.

We previously showed that IL-1 plays an important role in the enhancement of T cell–APC interactions through the induction of CD40L and OX40 on T cells (Nakae et al. 2001b). Consistently with this observation, CD40L and OX40 expression were enhanced in T cells stimulated with antigen-bearing IL-1Ra$^{-/-}$ APCs in comparison to WT APCs. On the other hand, ligation of CD40 on APCs by CD40L induces OX40L expression and TNFα production by APCs (van Kooten and Banchereau 2000; Weinberg 2002). Furthermore, we have demonstrated that TNFα induces OX40 expression on T cells (Horai et al. 2004). Thus, upon interaction with antigens, APCs produce IL-1. IL-1, in turn, activates T cells, resulting in the induction of CD40L. The CD40L-CD40 interaction induces APCs to produce OX40L and TNFα, resulting in the induction of OX40 on T cells. Therefore, it is suggested that TNFα plays an important role in the sensitization of T cells and contributes to the development of autoimmunity.

It is known that TNFα$^{-/-}$ mice lack splenic primary B cell follicles and cannot form either organized follicular dendritic cell (DC) networks or germinal centers in the spleen and peripheral lymphatic organs (Pasparakis et al. 1996). Prolonged antibody responses are generally impaired in TNFα$^{-/-}$ mice, although Ig class-switching is not completely deficient. It is therefore reasonable to suppose that these functions of TNFα in the humoral immune responses may also contribute to the development of autoimmunity in IL-1Ra$^{-/-}$ mice. However, since we could not induce arthritis by transferring IL-1Ra$^{-/-}$ mouse serum into WT mice, only a weak contribution of humoral immune responses is suggested in this animal model (Horai and Nakajima, unpublished results).

On the other hand, it is known that TNFα elicits inflammation by activating and recruiting inflammatory cells and inducing proinflammatory cytokines and chemokines, such as IL-1, IL-6, and CXCLIO (Pang et al. 1994; Nakae et al. 2003b). In this context, mouse models that exhibit higher amounts of TNFα protein, such as transgenic (Tg) mice carrying the TNFα gene or mice deficient for the TNFα AU-rich element (TNF$^{\Delta ARE}$), spontaneously develop arthritis (Keffer et al. 1991; Kontoyiannis et al. 1999). It was suggested that innate and/or stromal

mechanisms rather than T cell-mediated autoimmune mechanisms are involved in the development of arthritis, because arthritis develops in RAG1$^{-/-}$ background, although Crohn's-like disease is induced by an immune-mediated mechanism in the same model (Kontoyiannis et al. 1999). Likewise, inflammatory cytokines, such as IL-1 and TNFα, but not IL-6, play important roles in the effector phase of the disease in the K/BxN model, although the effect of TNFα deficiency was not as strong in this model compared to that seen in the IL-1Ra$^{-/-}$ mice (Ji et al. 2002). Taken together, these observations suggest that TNFα plays important roles in both sensitization of T cells and elicitation of inflammation in the development of arthritis in IL-1Ra$^{-/-}$ mice.

8.2.3 The Role of IL-17 in the Development of Arthritis

IL-17 levels in IL-1Ra$^{-/-}$ mouse joints were elevated from the levels seen in wild-type mice. After stimulation with CD3, IL-17 production was greatly enhanced in IL-1Ra$^{-/-}$ T cells (Nakae et al. 2003d). In our examination of the development of arthritis in IL-17$^{-/-}$ mice, we demonstrated that IL-17-deficiency completely suppressed the onset of disease in IL-1Ra$^{-/-}$ mice (Nakae et al. 2003d). Joint inflammation was also suppressed in IL-17$^{-/-}$-human T cell leukemia virus type I (HTLV-I) Tg mice carrying the HTLV-I *tax* gene, another RA model in which arthritis develops spontaneously (Iwakura et al. 1991; unpublished observation). An important role for IL-17 was also indicated in the CIA model (Nakae et al. 2003c). We have shown that, upon stimulation with ovalbumin (OVA), OVA-specific T cell proliferation was low in T cells from IL-17$^{-/-}$-DO11.10 mice (Nakae et al. 2002, 2003d), mice carrying an OVA-specific T cell receptor transgene. These results suggest that IL-17 is involved in T cell priming. Consistent with this notion, we demonstrated that the sensitization of T cells following immunization with type II collagen was significantly reduced in IL-17$^{-/-}$ mice (Nakae et al. 2003c). Nonetheless, since both the incidence and the severity score were reduced in IL-17$^{-/-}$ mice in CIA, IL-17 may function not only at the sensitization phase but also the elicitation phase.

As mentioned above, IL-1Ra production by T cells is critical in the regulation of T cell activity by acting on T cells in an autocrine manner

(Horai et al. 2004). It is known that IL-1 induces CD40L on T cells, and CD40 signaling activates TNFα expression in APCs (van Kooten and Banchereau 2000; Nakae et al. 2001b). Since the TNFα induces OX40 expression on T cells (Horai et al. 2004) and IL-17 production by T cells was induced by OX40 activation (Nakae et al. 2003d), TNFα-mediated induction of OX40 expression in T cells may induce production of IL-17, resulting in the exacerbation of inflammation. Thus, it was suggested that both CD40L-CD40 and OX40L-OX40 play important roles in the development of autoimmunity. In agreement with this notion, blockade of the CD40L–CD40 or OX40–OX40L interaction inhibited arthritis development in IL-1Ra$^{-/-}$ mice (Horai et al. 2004). These observations suggest that T cell-dependent autoimmunity is induced in IL-1Ra$^{-/-}$ mice through the induction of TNFα and IL-17, as the downstream mediators of the IL-1 action, and these cytokines also play important roles in the elicitation phase of inflammation (Fig. 3).

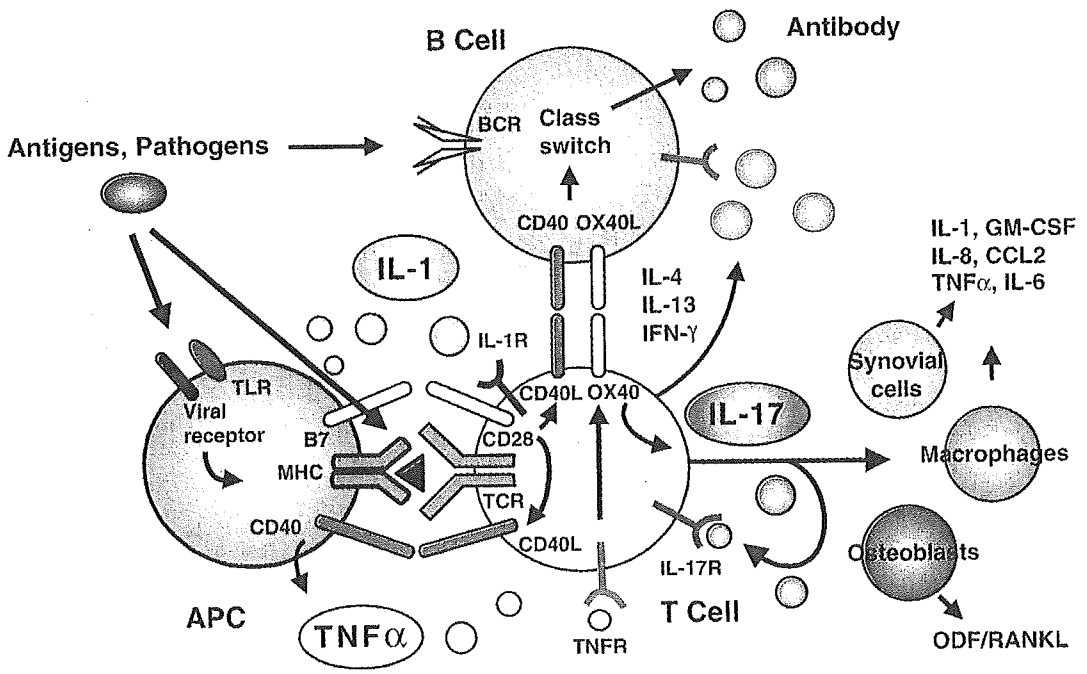

Fig. 3. Crucial roles for IL-17 and TNFα, downstream of IL-1 signaling, in the pathogenesis of arthritis

8.3 The Roles of TNFα and IL-17 in the Development of Aortitis

8.3.1 Development of Aortitis in IL-1Ra$^{-/-}$ Mice

IL-1Ra$^{-/-}$ mice on the BALB/c background spontaneously developed arterial inflammation at 4 weeks of age. Approximately 50% of the mice were affected by 12 weeks (Matsuki et al. 2005). A similar observation was reported in IL-1Ra$^{-/-}$ mice on the 129/Ola x MF1 background (Nicklin et al. 2000). On the C57BL/6 background, however, there were no signs of arterial inflammation, suggesting the significant involvement of background genes in the development of aortitis, a similar observation that has been made for arthritis (Horai et al. 2000). In F2 hybrids of BALB/c- and C57BL/6-IL-1Ra$^{-/-}$ mice, arthritis was rare but aortic inflammation was common, indicating that the sets of background modifier genes that cause susceptibility to each disease are not fully overlapping (Shepherd et al. 2004).

Inflammation of the cardiovascular system was observed preferentially at the aortic root of IL-1Ra$^{-/-}$ mice (Fig. 4) (Matsuki et al. 2005). The infiltration of monocytes and occasionally neutrophils was observed in the aorta and aortic valve. A loss of elastic lamellae in the aortic media could be observed by histological examinations. Monocytes/macrophages and some neutrophils had infiltrated the inflammatory sites within the aortic sinus. Thus, the aortic inflammation in these animals may have characteristics of both acute and chronic phases of disease. We identified numerous examples of neovascularization within severe lesions. Chondrocyte-like cells were observed in the majority of IL-1Ra$^{-/-}$ mouse aortas; no such cells could be observed in the aortas of WT mice. Calcification of the media of the aorta was observed in a subset of IL-1Ra$^{-/-}$ mice. As calcification of the media, involving the degradation of smooth muscle cells, is a sign of degenerative processes (Tanimura et al. 1986a, 1986b), this result suggests the involvement of an immune response in this pathology. These mice suffered from mild aortic stenosis and hyperplasia of the interventricular septum and left ventricular posterior walls. In agreement with previous reports, these pathological findings resemble aspects of Takayasu arteritis or polyarteritis nodosa in humans (Nicklin et al. 2000).

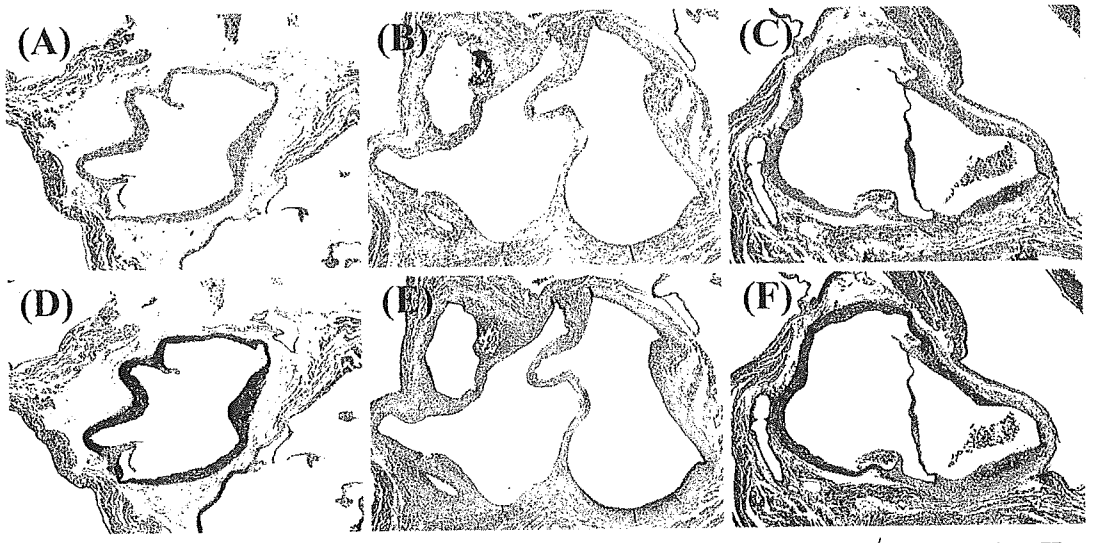

Fig. 4. Attenuation of the development of aortitis in IL-1Ra$^{-/-}$ mice by IL-17 deficiency. Sections of the aorta were examined by staining with (**A–C**) hematoxylin and eosin and (**D–F**) Masson's trichrome (Isoda et al. 2002). **A, D** Sections of the aortic valve (score 0) from a 20-week-old unaffected IL-17$^{+/-}$-IL-1Ra$^{-/-}$ mouse. **B, E** Sections from a 20-week-old affected IL-17$^{+/-}$-IL-1Ra$^{-/-}$ mouse. Severe inflammatory cell infiltration and loss of elastic lamellae over greater than two-thirds of the media of the aortic sinus are observed (score 3). **C, F** Sections from an 20-week-old IL-17$^{-/-}$-IL-1Ra$^{-/-}$ mice. Mild inflammatory cell infiltration and loss of elastic lamellae are observed (score 2)

Using peripheral T cell transplantation, we also examined the role of T cells in the development of aortitis (Matsuki et al. 2005). Purified T cells from the spleens and lymph nodes of 6- to 8-week-old IL-1Ra$^{-/-}$ mice were transplanted into BALB/c-*nu/nu* mice, and the development of aortitis in the recipient mice was analyzed 10 weeks after transplantation. Twelve of the 13 recipient mice developed aortitis, indicating that T cells are crucial in the pathogenesis of aortitis. As arthritis is also induced by IL-1Ra$^{-/-}$ T cell transplantation, the pathogenesis of aortitis likely utilizes a similar mechanism as that seen in arthritis, in which T cell-mediated autoimmunity caused by excess IL-1 signaling is involved.

8.3.2 The Roles of TNFα and IL-17 in the Development of Aortitis

We examined the roles of TNFα and IL-17 in the development of aortitis by intercrossing these cytokine-deficient mice to IL-1Ra$^{-/-}$ mice. The aortic valves of these cytokine-deficient IL-1Ra$^{-/-}$ mice were analyzed histologically. Interestingly, TNFα$^{-/-}$-IL-1Ra$^{-/-}$ mice showed no signs of arterial inflammation at 8 and 14 weeks of age, while approximately 50% of the TNFα$^{+/+}$-IL-1Ra$^{-/-}$ mice developed aortitis at these ages (Matsuki et al. 2005). The incidence of aortitis in IL-17$^{-/-}$-IL-1Ra$^{-/-}$ mice was similar to IL-17$^{+/-}$-IL-1Ra$^{-/-}$ mice at 20–28 weeks of age (Table 2). The disease severity score, however, was significantly reduced in these IL17$^{-/-}$-IL-1Ra$^{-/-}$ mice (Fig. 4). Thus, in IL-1Ra$^{-/-}$ mice, TNFα is crucial for the development of aortitis. While IL-17 is not essential for aortitis development, it aggravates the disease, appearing to function at both the elicitation of inflammation and the sensitization of T cells.

As mentioned already, we have demonstrated that T cell-derived TNFα plays an important role for the sensitization of T cells in the development of autoimmunity in IL-1Ra$^{-/-}$ mice (Horai et al. 2004). Other investigators have also reported the production of TNFα in T cells (Ramshaw et al. 1994; Sakaguchi et al. 1995) and the presence of TNF receptors in aortic smooth muscle and endothelial cells (Field et al. 1997). Thus, upon T cell activation, T cells produce TNFα, and this T-cell derived TNFα may activate endothelial cells to produce various

Table 2. Suppression of the development of aortitis in IL-17$^{-/-}$-IL-1Ra$^{-/-}$ mice

Genotype	Incidence (%) Severity score 20, 28 weeks
IL-17$^{+/-}$-IL-1Ra$^{-/-}$	5/6 (83%) 2.8
IL-17$^{-/-}$-IL-1Ra$^{-/-}$	6/13 (46%) 1.8*

* $p < 0.05$ vs IL-17$^{+/-}$-IL-1Ra$^{-/-}$ mice by Mann-Whitney U test

inflammatory cytokines and chemokines, resulting in the development of inflammation (Kollias and Kontoyiannis 2002). It is also known that TNFα induces the expression of vascular cell adhesion molecule-1 in endothelial cells; this promotes the early adhesion of mononuclear leukocytes to the arterial endothelium at sites of inflammation (Feldmann 2002).

Consistent with our observations, it was recently reported that Infliximab, an anti-TNFα antibody, improved endothelial dysfunction in antineutrophil cytoplasmic antibody-associated systemic vasculitis in humans (Booth et al. 2004). Although the etiopathogenesis of this vasculitis has not been completely elucidated, it is thought that both aortitis in IL-1Ra$^{-/-}$ mice and antineutrophil cytoplasmic antibody-associated systemic vasculitis in humans share a similar pathogenic process involving TNFα. These observations provide new insight into the pathogenesis of vasculitis, and the IL-1Ra$^{-/-}$ mice should be a useful model for the study of the pathogenic mechanisms of vasculitis (Fig. 5).

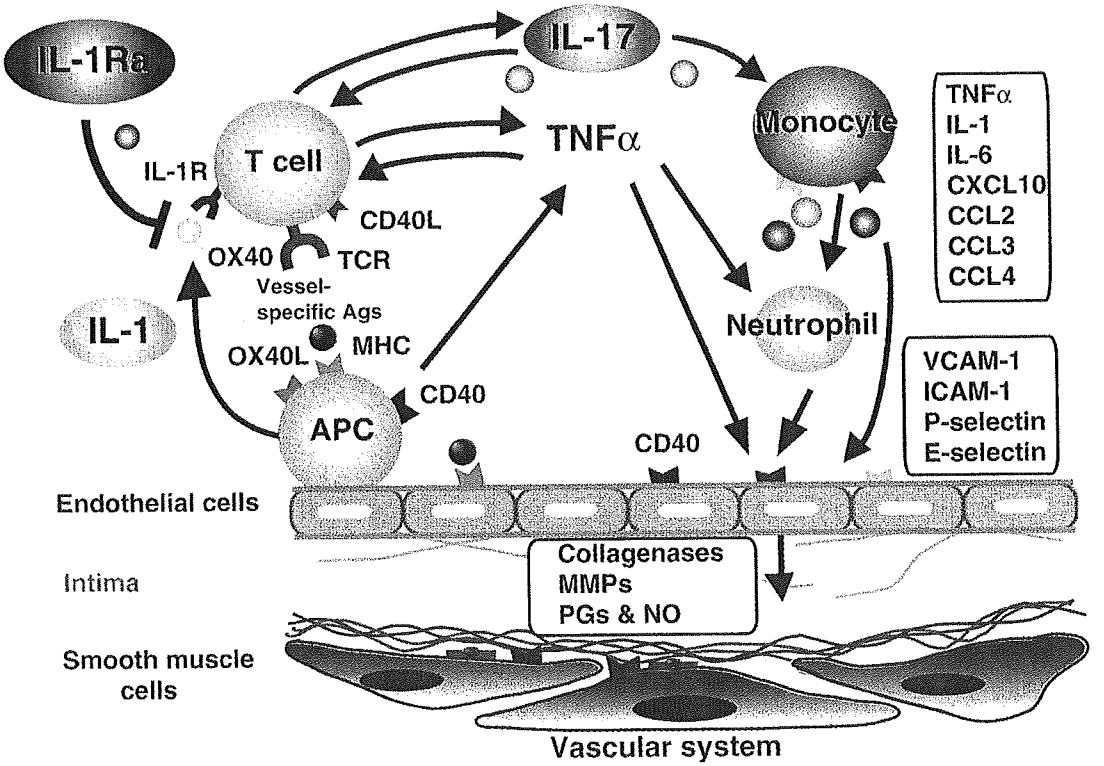

Fig. 5. Pathogenesis of aortitis: TNFα plays an important role in the development of aortitis in IL-1Ra$^{-/-}$ mice

8.4 The Role of TNFα in the Development of Dermatitis

8.4.1 Development of Psoriasis-Like Dermatitis in IL-1Ra$^{-/-}$ Mice

Psoriasis-like skin disease, first reported by Shepherd et al. (2004), was evident in IL-1Ra$^{-/-}$ mice on the BALB/c background. However, we could not identify disease in animals on the C57BL/6 background, indicating that strain-specific background genes are also involved in the development of this disease. The mice on the BALB/c background develop redness and scaling of their ears and tail (Fig. 6), a pathology characterized by extensive thickening of the epidermis associated with hyperkeratosis of the skin. The majority of keratinocytes retained their nucleus in the cornified cellular layer. We also observed massive neutrophil infiltration into the epidermis and dermis. With increasing disease progression, the epidermal layer gradually penetrated into the dermal layer, forming ridges. Aseptic microabscesses formed under the skin. CD4$^+$ T cells were occasionally observed within the dermis.

Interestingly, however, significant disease developed in *scid/scid*-IL-1Ra$^{-/-}$ mice. Furthermore, IL-1Ra$^{-/-}$ T cell transfer could not induce dermatitis in *nu/nu* mice, in contrast to cases of arthritis or aortitis in

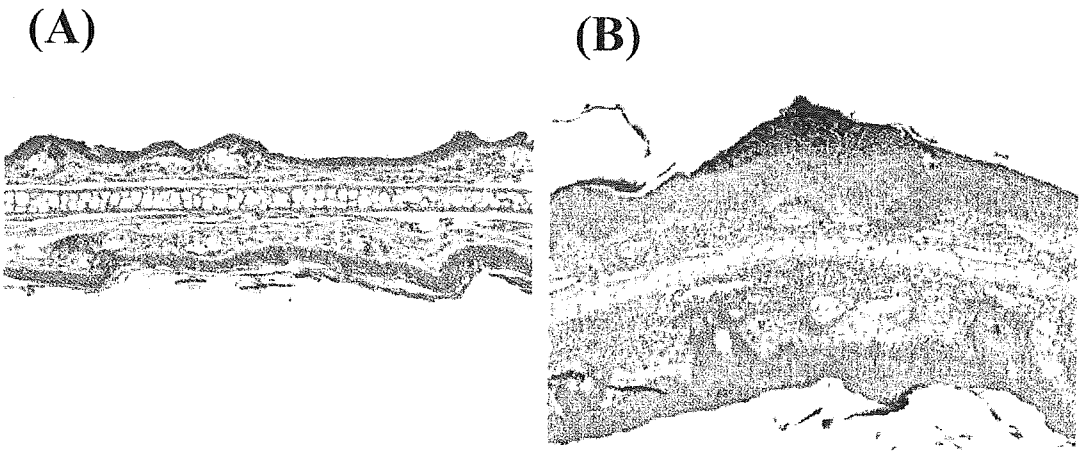

Fig. 6. Histological examination of the skin in IL-1Ra$^{-/-}$ mice. **A** Hematoxylin and eosin staining of the ear pinna of a normal 20-week-old WT mouse. **B** An affected IL-1Ra$^{-/-}$ mouse at 20 weeks of age. The epidermis becomes thickened and hypertrophic associated with hyperkeratosis of the skin. Massive infiltration of neutrophils into the epidermis and dermis are observed in IL-1Ra$^{-/-}$ mouse

which diseases could be induced by T cell transfer. Thus, in this case, an autoimmune process is not likely to be involved in disease pathogenesis; rather, excess IL-1 signaling directly induces inflammation within the skin.

In humans, the involvement of IL-1 in the development of psoriasis has not been elucidated completely. Some studies have indicated that IL-1α concentrations were reduced in psoriatic lesional skin as compared to nonlesional and normal skin, although IL-1β concentrations were increased (Cooper et al. 1990; Debets et al. 1997). Our data clearly show that excess IL-1 signaling can induce psoriasis-like lesions in mice, suggesting involvement of IL-1 in the development of psoriasis in humans. In agreement with our observations, Tg mice that express IL-1α from K14 promoter in the basal epidermis also develop scaly and erythematous inflammatory skin lesions (Groves et al. 1995).

8.4.2 The Role of TNFα in the Development of Dermatitis

The development of dermatitis in IL-1Ra$^{-/-}$ mice was completely absent in TNFα-deficient IL-1Ra$^{-/-}$ mice, indicating a crucial role for TNFα in disease pathogenesis. The importance of IL-1 and TNFα were also seen in contart hypersensitivity (CHS) reactions, in which antigen-specific CD4^{+} T cells play a central role. 2, 4, 6-trinitrochlorobenzene (TNCB)-induced CHS was suppressed in IL-1α/β$^{-/-}$ and IL-1α$^{-/-}$, but not IL-1β$^{-/-}$, mice, and these responses were augmented in IL-1Ra$^{-/-}$ mice, suggesting an important role for IL-1α in CHS responses (Nakae et al. 2001c, 2003b). We demonstrated that the IL-1 produced by APCs of the epidermis enhances the sensitization of allergen-specific T cells and induces inflammation via TNFα production during the elicitation phase (Nakae et al. 2003b). TNFα elicits inflammatory cell infiltration in the skin through the induction of CXCLIO.

TNFα production is increased in psoriatic lesional skin as compared to nonlesional and healthy skin (Ettehadi et al. 1994). Moreover, direct correlation between TNFα concentration either at the lesional skin or serum levels and the psoriasis area severity index scores has been reported (Bonifati et al. 1994). Thus, TNFα may also be involved in the development of psoriasis in humans (Fig. 7).

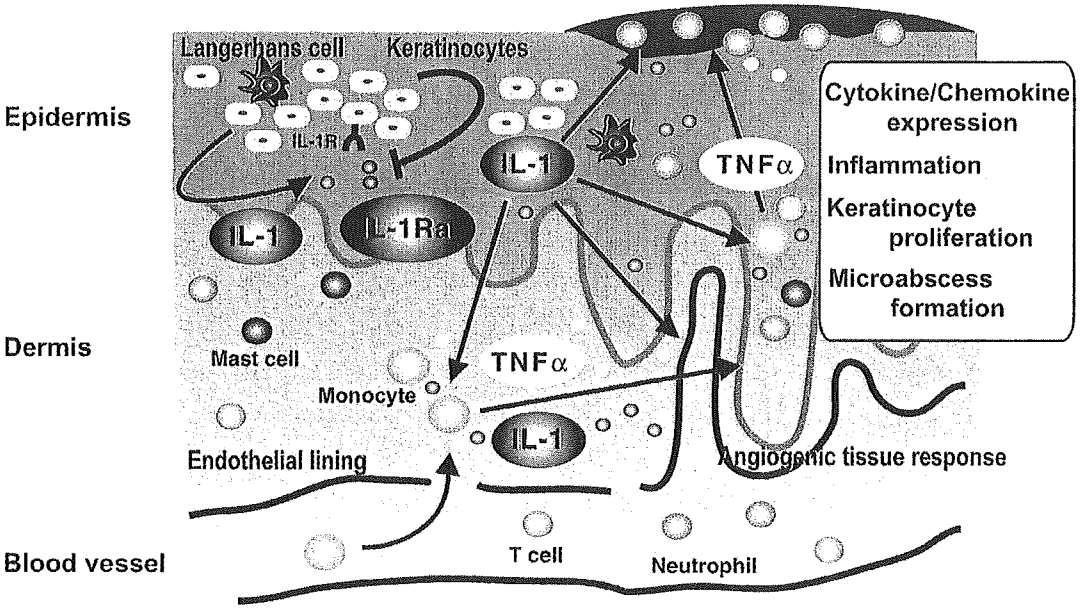

Fig. 7. Pathogenesis of dermatitis

In human psoriasis, the importance of an acquired immune response is suggested, because linkage association with MHC class I is observed (Elder et al. 1994), the dermis and the epidermis are heavily infiltrated by $CD4^+$ T cells (Baker and Fry 1992), cyclosporin A efficiently suppresses psoriasis (Griffiths et al. 1989), and depletion of $CD25^+$ T cells ameliorates the disease (Gottlieb et al. 1995). Furthermore, it was shown that injection of prepsoriatic skin engrafted onto *scid/scid* mice with $CD4^+$ T cells induces psoriasis (Nickoloff and Wrone-Smith 1999). However, so far, no conclusive evidence has been presented for the involvement of autoimmunity in this disease. On the other hand, it has been argued that keratinocytes of psoriatics suffer from an intrinsic abnormality in the regulation of their activation by cytokines, which trigger proliferation and migration, and stimulated keratinocytes may act as initiators of an inflammatory process by means of the secretion of various cytokines able to induce the expression of cell adhesion molecules and the recruitment of inflammatory cells (Bonifati and Ameglio 1999; Shepherd et al. 2004). Our observations suggest that keratinocyte-derived pathogenesis rather than an autoimmune mechanism is involved in the development of dermatitis in IL-$1Ra^{-/-}$ mice. Since the infiltration of inflammatory cells is not prominent at the beginning of the disease and gradually increases, immune mechanisms may be involved at the later phase.

8.5 Conclusion

We have demonstrated that a variety of inflammatory diseases, including arthritis, aortitis, and psoriatic dermatitis, develop spontaneously in IL-1Ra$^{-/-}$ mice. Although excess IL-1 signaling is responsible for the development of these diseases, the pathogenic mechanisms differ significantly; both arthritis and aortitis result from the development of autoimmunity, while such autoimmune processes are not involved in the development of dermatitis. Both TNFα and IL-17 play important roles in the activation of T cells downstream of IL-1 signaling, in addition to the roles in the elicitation of inflammation. TNFα activates T cells by inducing OX40 expression, leading to increased IL-17 production. Although IL-17 was also shown to be involved in the sensitization of T cells, the mechanism underlying this activation remains to be elucidated. Thus, both cytokines play crucial roles in the development of the autoimmunity that can cause arthritis and aortitis in this knockout mouse model. In contrast, in the case of psoriatic dermatitis, excess IL-1 signaling and TNFα signaling directly induce inflammation of the skin without the involvement of autoimmunity. Thus, IL-1 and TNFα have dual functions, the activation of T cells and the direct induction of inflammation. It is interesting that excess IL-1signaling can induce several different diseases in an animal via different mechanisms. In any case, these observations suggest that the suppression of IL-1, TNFα, and IL-17 is important in the control of inflammatory diseases; suppression of cytokine expression or action should be beneficial for the treatment of these diseases.

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