J. Clin. Exp. Hematopathol
Vol. 44, No. 1, Apr 2004

Review Articles

Pleiotropic Role of AIM in Lymphocyte Apoptosis and Inflammation

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Apoptosis of cells must be managed both positively and negatively in response to various environmental stresses via differential signal transduction cascades. Recently, an apoptosis inhibitor expressed by macrophages (AIM) was presented as a novel murine soluble protein. AIM is a member of the macrophage scavenger receptor, cysteine-rich domain superfamily (SRCR-SF), which shares a highly homologous-conserved, cysteine-rich domain. AIM inhibits the apoptosis of $CD4^+CD8^+$ (CD4/CD8) double-positive (DP) thymocytes, and supports the viability of these cells in T cell development in the thymus. In inflammatory sites outside the thymus, AIM appears to enhance macrophage phagocytosis, inhibit B cell proliferation in combination with transforming growth factor-β and inhibit apoptosis of natural killer T (NKT) and natural killer (NK) cells. AIM thus has diverse functions that depend on the type of target cell and its combination with other cytokines.

Key words apoptosis inhibitor expressed by macrophages (AIM), inflammation, lymphocytes, macrophages.

INTRODUCTION

Two forms of cell death, necrosis and apoptosis, have been described in vertebrate tissues. While necrosis is a pathologic response, apoptosis is a more subtle process that commonly occurs when cell death is physiologically determined[1-4]. Apoptosis represents cell death via programmed signal cascades in the developing embryo during morphogenesis and in adults during cell turnover, thymocyte development, or at the end of an immune response. Thus, apoptosis is involved in diverse physiological conditions, and disturbed apoptosis may contribute to various diseases, such as cancer, autoimmunity, and degenerative disorders[5-9]. The balance of positive (inducing) and negative (inhibitory) regulation of apoptosis may also critically influence progression of inflammation[10-13]. The positive regulation of apoptosis has gradually been clarified[14-23]. However, the negative regulation of apoptosis has essentially been ignored. Miyazaki et al. recently isolated a novel murine soluble molecule, termed AIM, which is secreted exclusively by tissue macrophages and is associated with the negative regulation of apoptosis. AIM was first recognized as an apoptosis inhibitor of $CD4^+CD8^+$(CD4/CD8) double-positive (DP) thymocytes. AIM supports the viability of thymocytes before thymic selection[24]. However, AIM appears to have pleiotropic functions that include inhibition of apoptosis in a variety of cell types, particularly at inflammatory sites. In this review, we present the biological profile and functions of AIM.

Received : Oct 7, 2003
Revised : Dec 11, 2003
Accepted : Dec 11, 2003

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MOLECULAR STRUCTURE OF AIM

AIM was originally identified, in 1998, as a member of the macrophage scavenger receptor, cysteine-rich domain superfamily (SRCR-SF)[24]. SRCR-SF cell-surface and/or secreted proteins have a highly conserved, cysteine-rich domain

(SRCR domain). The SRCR domain, which consists of approximately 100 residues containing 6–8 cysteines, was first reported in the macrophage scavenger receptor type I. AIM contains three SRCR domains[24], each of which is well conserved in other SRCR-SF members. Each member of the SRCR-SF appears to have different functions. No consensus role for the SRCR domain has been established and no other SRCR-SF members are known to be involved in the inhibition of apoptosis, reflecting the diverse functions of SRCR-SF member molecules.

AIM is located on murine chromosome 3 and its messenger ribonucleic acid (mRNA) is 1947 bp (full length, GenBank Accession No. AF0114248)[24]. The amino acid sequence of mouse AIM has a potential leader sequence prior to the three SRCR domains and four exon-intron junctions[24]. AIM has features of a 54-kD secreted protein characterized by a potential signal-peptide sequence, and no transmembrane-like hydrophobic regions[24].

EXPRESSION OF AIM

In non-treated, wild type mice, AIM mRNA expression is weakly detected in the spleen, liver and thymus. However, AIM is rapidly expressed by murine tissue macrophages in response to inflammatory stimuli[24–26]. We have observed that AIM is expressed in a subset of macrophages in *Corynebacterium parvum (C. parvum)*-induced hepatic granulomas[26], while the expression of AIM mRNA in the liver of non-treated mice is weak. After *C. parvum* injection, AIM expression was enhanced and reaches a maximum level at day 10, followed by a gradual decrease. AIM-expressing cells, Kupffer cells and macrophages, were also scattered in the sinusoid and the periphery of granulomas in our study. No expression of AIM mRNA was found in endothelial cells or hepatocytes. It appears that AIM may play a negative regulatory role in inflammatory sites, because AIM mRNA is not expressed in any of the liver cells in AIM-knockout mice, which show a more fulminant clinical course than wild type mice. Thus, AIM has been suggested to exhibit anti-inflammatory functions in granulomatous inflammation.

We also observed that AIM was expressed in a subset of macrophages in bacillus Calmette Guérin (BCG)-induced hepatic granulomas[24], where it was expressed in macrophages at the periphery of the granulomas, but not in macrophages found at the central area of granulomas. In addition, AIM was expressed in a subset of, but not all, Kupffer cells and macrophages. In the thymus, AIM mRNA expression was observed in a subpopulation of macrophages in the cortex, but was not detected in medullary macrophages after BCG-injection. In the spleen, AIM mRNA was expressed predominantly by macrophages in the marginal zone. Alternatively, cell-cell interaction between macrophages and specific types of cells in tissues and/or a specific microenvironment is required to induce AIM expression in macrophages. AIM mRNA was expressed strongly in thioglycolate-elicited peritoneal macrophages isolated from recombination activating gene (RAG)-$2^{-/-}$ mice. However, AIM expression disappeared completely once these cells were cultured on plastic dishes for 16 h, and expression could not be reinduced by phorbol myristate acetate (PMA), lipopolysaccharide (LPS), or several cytokines, including interferon-gamma (IFN-γ). Thus, AIM has also been suggested to exhibit different functions for various types of target cells in combination with other cytokines.

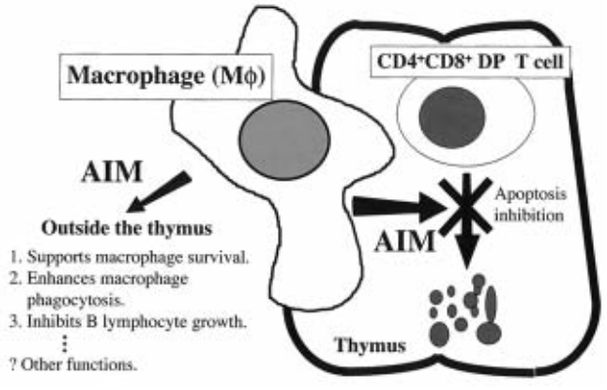

Fig. 1. Diverse functions of AIM.
In the thymus, AIM inhibits the apoptosis of thymocytes, especially CD4/CD8 DP thymocytes, and supports the viability of these cells before thymic selection. Outside the thymus, AIM supports macrophage survival, enhances macrophage phagocytosis and inhibits B lymphocyte growth. Moreover, AIM seems to have other, as yet unidentified, functions.

AIM AS AN APOPTOSIS INHIBITOR OF LYMPHOCYTES

In the thymus, thymic small lymphocytes, commonly known as thymocytes, are highly radiosensitive. Immature thymocytes, such as CD4/CD8 DP T cells, easily undergo apoptosis within a few hours after irradiation[27–29] or administration of a glucocorticoid[30–34]. AIM appears to function as an apoptosis inhibitor for thymocytes, especially for CD4/CD8 DP thymocytes, and supports viability of these cells before thymic selection (Fig. 1)[24].

AIM-mediated inhibition of CD4/CD8 DP thymocyte apoptosis in thymic selection revealed two major physiological processes. In the medulla of the thymus, upregulation of Bcl-2 expression in single-positive (SP) cells after positive selection strongly saved SP cells from apoptotic cell death[35–37]. In the cortex of the thymus, AIM secreted by thymic macrophages protects DP thymocytes from apoptotic cell death until they are positively selected. AIM acts to decrease DP thymocyte susceptibility to apoptosis. Cortical macrophages form "rosettes" with the DP thymocytes in the thymus[38,39]. DP thymocytes in the rosettes are selectively protected from apoptosis both *in vivo* and *in vitro*[40]. Cortical macrophages in the thymus may directly or indirectly support the viability of the associated DP thymocytes via AIM. Macrophages also induce death within DP thymocytes via MHC-TCR interactions or by secreting various effectors[41]. Therefore, macrophages might regulate DP thymocyte apoptosis by mediating either positive or negative signals, depending on stimuli in the microenvironment.

Inhibition of apoptosis by AIM *in vitro* suggests that the inhibitory effect of AIM on apoptosis is more general. AIM could be involved in the negative regulation of, not only DP thymocyte apoptosis, but also that of other types of cells to which AIM binds in specific microenvironments where AIM expression is induced in macrophages. Although extracellular apoptosis inhibitory elements have not been defined clearly, AIM also appears to mediate inhibitory signals for the apoptosis of some inflammatory cells and to modulate the inflammatory process. For instance, AIM inhibits B lymphocyte proliferation with transforming growth factor-β1 (TGF-β1) *in vitro*. The resulting major effects on activated B cells are immunoglobulin class switching towards IgA and IgG and cell growth inhibition, resulting in an almost complete block of proliferation and immunoglobulin secretion. TGF-β1 appears to increase the expression of AIM receptors on the B cell surface[42]. NKT cells, which are very sensitive to apoptosis[43,44], seem to be regulated by AIM in hepatic granuloma. Moreover, AIM may have pleiotropic functions that inhibit the apoptosis of a variety of cell types, particularly at inflammatory sites.

Fas/Fas ligand (Fas/Fas L) interactions promote activation-induced death of NKT lymphocytes[43]. On the other hand, in a lymphocytic choriomeningitis virus (LCMV) model, NKT cells were lost via apoptosis independently of IFN-γ and interleukin 12 (IL-12) production, or levels of CD28 and Fas/Fas L. NKT apoptosis could be due to the induction of IFN-α/β. In our recent study, we considered whether Fas/Fas L interactions acted in the apoptosis of NKT lymphocytes[26]. However, this remains uncertain and a problem to be solved in future studies.

AIM AS A REGULATOR OF MACROPHAGES

AIM exhibits several negative regulatory functions for various types of target cells in granuloma formation. For instance, in *C. parvum*- and LPS-induced hepatitis, AIM inhibits the death of macrophages in the inflammatory regions, judging by the remarkably increased number of macrophages observed in the liver of AIM transgenic mice[25]. In other words, AIM is associated with hepatitis by supporting macrophage survival at inflammatory sites via inhibitory effects on apoptosis, which may contribute to efficient clearance of dead cells and toxic reagents by macrophages. AIM revealed two different functions for macrophages : apoptosis inhibition of T cells and NKT cells, and enhancement of the phagocytizing function toward *C. parvum*[26]. This multifunctional character of AIM is similar to that of various cytokines, such as interleukin-4 (IL-4)[46].

After *C. parvum* injection, the production of monocyte chemoattractant protein (MCP)-1 was enhanced in the liver of AIM-knockout mice in which granuloma formation is more remarkable

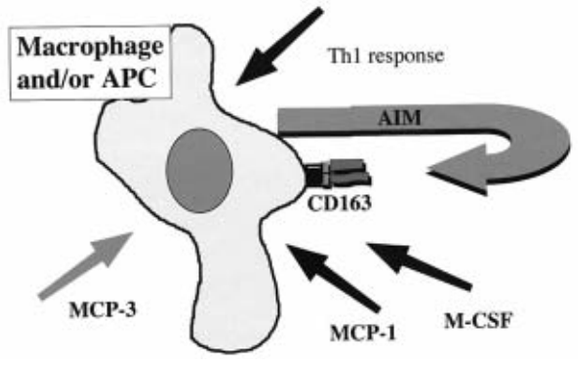

Fig. 2. Role of AIM in macrophage activation after *C. parvum* injection.

AIM induces the production of chemokines that enhance macrophage functions including phagocytosis and migration. The Th1 response, which is strongly produced by overactive macrophages, and a storm of cytokines in AIM-knockout mice seems to recruit more monocytes and macrophages into the granulomas of AIM-knockout mice (black arrow). MCP-1 has the strongest migration activity in monocytes. M-CSF and MCP-3 also activate migration and proliferation of monocytes and macrophages. MCP-1 and M-CSF are strongly expressed in the liver of AIM-knockout mice (black arrows). MCP-3 is slightly increased at the late phase of granuloma formation (gray arrow). AIM seems to be associated with the inhibition of macrophage activation in an autocrine fashion, via CD163, which has significant similarity to AIM (gray arrow with black shadow).

than in wild-type mice[26]. MCP-1 has the strongest migration activity for monocytes at the lowest serum concentration of all the cytokines and is secreted from macrophages due to inflammation and actions of various cytokines, such as interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-α), and IFN-γ. Furthermore, macrophage-colony stimulating factor (M-CSF) and MCP-3 were increased at the late phase of granuloma formation. M-CSF and MCP-3 have migration and proliferation activities against monocytes and macrophages[47]. The Th1 response, overactive macrophages and a storm of cytokines, seemed to recruit more monocytes and macrophages into the granulomas of AIM-knockout mice. These data suggest that chemokine production is associated with the functions of AIM. A homology search in the public databases revealed that the product of the AIM gene has significant similarity to CD163, a macrophage surface marker and a member of the SRCR-SF. CD163 is expressed on most macrophage lineages, including peripheral blood monocytes and tissue macrophages, and is thought to act as a regulator of the inflammatory response of these cells. AIM, a secreted protein, seems to be associated with the inhibition of macrophage activation in an autocrine fashion via CD163[48,49]. AIM may induce the production of cytokines that enhance macrophage phagocytosis (Fig. 2). However, we could not detect any up-regulation of the expression of these cytokines in macrophages after administration of AIM *in vitro*[26]. It is possible that unknown factor (s) may be induced by AIM. Further studies are necessary to define the regulatory functions of AIM in chemokine production and the activation of macrophages.

ROLE OF AIM IN GRANULOMATOUS INFLAMMATION

a. *AIM as a regulator of granuloma formation*

A granuloma is an organic cluster of lymphocytes and macrophages that includes epithelioid cells and giant cells. It is a chronic tissue reaction induced by various intrinsic or exogenous pathogens (Fig. 3)[50–52]. On average, it takes 14 days for a granuloma to form. In the liver, Kupffer cells and resident macrophages become activated, then differentiate and proliferate. Monocytes in the peripheral blood migrate and aggregate in the lesions. These granuloma lesions expand with the participation of monocytes, Kupffer cells and various types of lymphocytes. Epithelioid cells and giant cells formed by the fusion of macrophages sometimes appear in the granulomas. Granuloma formation is also a type of inflammatory process that can be accompanied by the production of several cytokines and chemokines[53–60]. M-CSF and granulocyte-macrophage colony-stimulating factor (GM-CSF) induce macrophage differentiation, and MCP-1 recruits monocytes to the inflamed lesion. IFN-γ, IL-4 and TNF-α produced by lymphocytes in the granuloma induce the activation of macrophages and naive T cells (Th0). Because AIM is expressed in Kupffer cells and macrophages in the sinusoid and the granulomas[24,26] (Fig. 3), it may play an important role in the interaction between macrophages and lymphocytes.

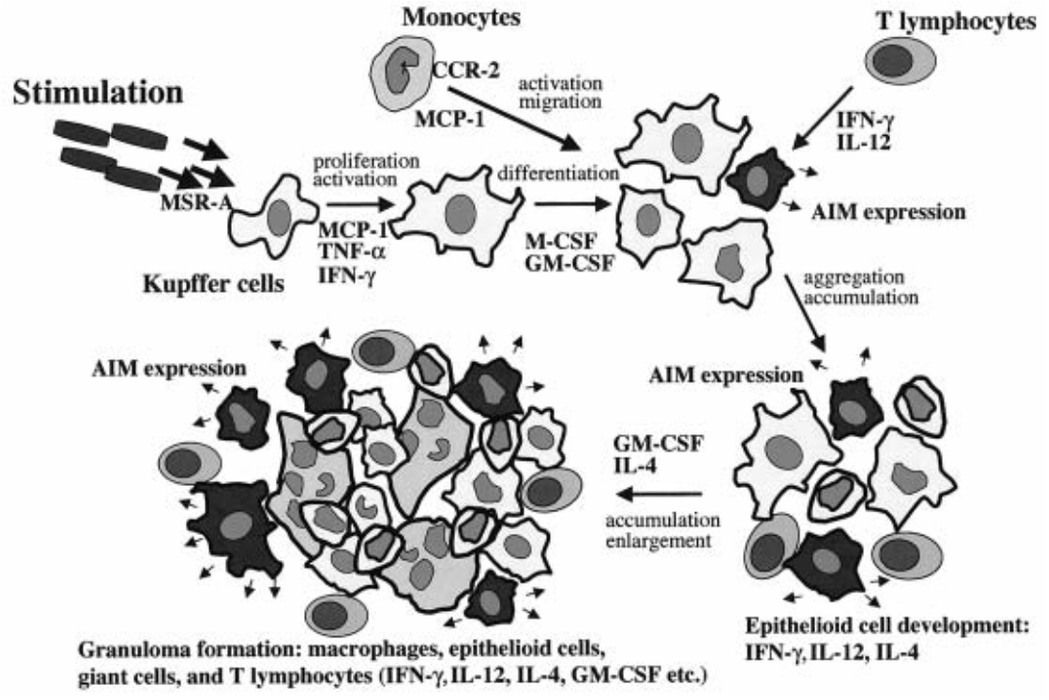

Fig. 3. Interactions among inflammatory cells in hepatic granuloma formation.
In the liver, Kupffer cells and resident macrophages are activated, then differentiate and proliferate in response to various stimuli. The monocytes in the peripheral blood invade the stimulated lesions. The granuloma lesions involving monocytes and Kupffer cells expand with the participation of various types of lymphocytes, epithelioid cells and/or giant cells which are formed by the fusion of macrophages. Granuloma formation is also a kind of inflammatory process that is accompanied by the production of several cytokines and chemokines. M-CSF and GM-CSF induce macrophage differentiation, and MCP-1 recruits monocytes to the inflamed lesion. IL-4, IFN-γ and TNF-α produced by lymphocytes induce macrophage activation and the Th0 switching cascade. Within the granulomas, AIM is definitely expressed (small arrows) in Kupffer cells and activated macrophages. AIM may play an important role in the interaction between macrophages and lymphocytes in granulomas, which are organic clusters of lymphocytes and macrophages that include epithelioid cells and giant cells, and represent a chronic tissue reaction induced by various intrinsic or exogenous pathogens.

b. *Increased apoptosis of NKT cells and prolonged granulomatous inflammation in AIM-deficient mice*

Macrophages and lymphocytes play a central role in inflammation[50−52]. AIM appears to inhibit apoptosis for NKT cells and T lymphocytes in *C. parvum*-induced hepatic granuloma formation[26]. In inflammatory sites, NKT cells are associated with enhanced antigen production, counteraction of parasite infestation, delayed hypersensitivity, anti-virus and anti-cancer activity, and transplantation immunity via Th1 or Th2 cell activation. IL-12 secreted from activated antigen-presenting cells (APC) that are resident macrophages and/or dendritic cells from and glycosylphosphatidylinositol (GPI) stimulate NKT cells. The activated NKT cells can produce IL-4 and IFN-γ. IL-4 promotes Th2 differentiation from Th0, while IFN-γ induces Th1 differentiation from Th0[61−66]. Meanwhile, IL-12 supports the activation, differentiation and proliferation of NK and NKT cells[67,68]. Thus, the dynamics of IL-12, IL-4, IFN-γ, NK cells and NKT cells are important interacting elements in inflammation.

The cytokine profiles from our previous study indicated that NKT and/or NK cells are closely involved with *C. parvum*-induced granulomatous inflammation[26]. In AIM-knockout mice, NKT cells were remarkably diminished. Therefore, IL-12 secreted from activated macrophages may only stimulate NK

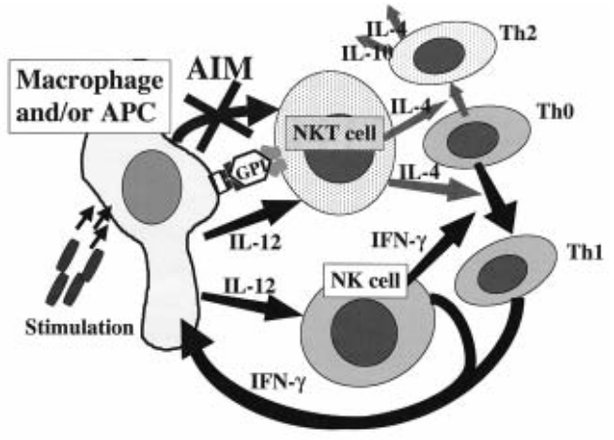

Fig. 4. Relationship between increased apoptosis of NKT cells induced by AIM deficiency and prolongation of granulomatous inflammation.

In general inflammatory sites, glycosylphosphatidylinositol (GPI) and IL-12 secreted from activated antigen-presenting cells (APC) stimulate NKT cells. Meanwhile, IL-12 supports the activation, differentiation and proliferation of NK cells. The activated NKT cells promote Th2 differentiation from Th0 via IL-4 production, and induce Th1 differentiation from Th0 via IFN-γ production. In AIM-knockout mice, IL-12 secreted from activated macrophages may only stimulate NK cells because NKT cells undergo remarkable apoptosis without AIM production from macrophages (black arrow with cross). Activated NK cells should also secrete IFN-γ, and promote Th1 differentiation via this IFN-γ. Hence, the relative activation of NK cells by diminishing NKT cells seems to enhance the Th1 type response in AIM-knockout mice. (Spotted cytoplasm : depressed cells ; gray cytoplasm : activated cells ; hatched arrows : down-regulation ; black arrows : up-regulation).

cells. Activated NK cells should also secrete IFN-γ, which would further stimulate the macrophages. NK cells are able to promote Th1 differentiation via IFN-γ, and NKT cells modulate switching from Th0 to Th1 or Th2 by secreting IFN-γ or IL-4, respectively[62,64,65]. The low or equal levels of interleukin-10 and IL-4 expressions found in the liver and serum of AIM-knockout mice suggest that switching from Th0 to Th2 is not induced efficiently due to the diminished NKT cells. Hence, it seems reasonable to consider that the diminished NKT cells enhanced the Th1 type response in AIM-knockout mice (Fig. 4). The higher IFN-γ mRNA expression in the liver and higher IFN-γ serum concentration in AIM-knockout mice may support this assumption[26].

Recently, a subset of dendritic cells that includes human monocyte (pDC1)-derived dendritic cells (DC1) and $CD4^+CD3^-CD11c^-$ plasmacytoid cells (pDC2)-derived dendritic cells (DC2) has been reported[69]. DC1 were found to induce Th1 differentiation via IL-12. Although DC2 induced Th2 differentiation by a mechanism that was unaffected by IL-4 or IL-12, this mediator has not yet been identified. AIM might regulate this mechanism between DC2 and Th2 differentiation via NKT cell apoptosis.

We found a new AIM function as an apoptosis inhibitor for NKT cells. Diminished NKT cells seemed to provide a cytokine storm and Th1-type response in AIM-deficient mice. Among factors that induce NKT cell recruitment, macrophage inflammatory protein-2 (MIP-2) has recently been reported to recruit NKT cells to the spleen during tolerance induction[70], and the number of NKT cells increased in **cryptococcal** infection in an MCP-1-dependent manner[71]. Further studies are necessary to clarify the regulatory role of AIM in the production of chemokines that recruit macrophages and NKT cells.

CONCLUSION

This review introduced the pleiotropic role of AIM in lymphocyte apoptosis and inflammation. AIM is also suggested to exhibit different functions for various types of target cells in combination with the effects of several cytokines. Further studies are necessary to define the regulatory functions of AIM in chemokine production and in the activation of various types of target cells.

ACKNOWLEDGMENTS

This study was supported in part by Grants-in-Aid for Scientific Research from the Ministry of Education, Science and Culture of Japan.

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