Association of AIM, a Novel Apoptosis Inhibitory Factor, with Hepatitis via Supporting Macrophage Survival and Enhancing Phagocytic Function of Macrophages*

Ikuko Haruta‡, Yoichiro Kato§, Etsuko Hashimoto‡, Christina Minjares¶, Shawna Kennedy¶, Hirofumi Uto‡, Katsumi Yamauchi‡, Makio Kobayashi‡, Sei-ichi Yusa**, Urs Müller‡, Naoaki Hayashi‡, and Toru Miyazaki‡‡

From the ‡Institute of Gastroenterology and §Department of Pathology, Tokyo Women’s Medical University, 8-1 Kawata-cho, Shinjuku-ku, Tokyo 162-8666, Japan, ¶Center for Immunology, The University of Texas Southwestern Medical Center, Dallas, Texas 75390-9093, ¶The Basel Institute for Immunology, Grenzacherstrasse 487, CH-4005 Basel, Switzerland, and **Fox-Chase Cancer Center, Philadelphia, Pennsylvania 19111

A hallmark of many inflammatory diseases is the destruction of tissue cells by infiltrating hematopoietic cells including lymphocytes, neutrophils, and macrophages. The regulation of apoptosis of both target tissue cells and the infiltrating cells is one of the key events that defines the initiation and the progression of inflammation. However, the precise picture of the apoptosis regulation of the cells at the inflammatory sites is still unclear. We recently isolated a novel apoptosis inhibitory factor, termed AIM, which is secreted exclusively by tissue macrophages. In this report, we present unique characteristics of AIM associated with liver inflammation (hepatitis), identified by introducing an experimental hepatitis in both AIM-transgenic mice, which overexpress AIM in the body, and normal mice. First, endogenous AIM expression in macrophages is rapidly increased in response to inflammatory stimuli. Second, AIM appears to inhibit the death of macrophages in the inflammatory regions, judging by the remarkably increased number of macrophages observed in the liver from transgenic mice. In addition, we show that AIM also enhances the phagocytosis by macrophages, which emphasizes the multifunctional character of AIM. All these findings strongly provoke an idea that AIM may play an important role in hepatitis pathogenesis in a sequential manner; first AIM expression is up-regulated by inflammatory stimuli, and then in an autocrine fashion, AIM supports the survival of infiltrating macrophages as well as enhances phagocytosis by macrophages, which may result in an efficient clearance of dead cells and infectious or toxic reagents.

Apoptosis is a form of cell death that is achieved by programmed signal cascades triggered by differential stimuli depending on the variety of physiological situations (1–4). Accumulating evidence has revealed that apoptosis plays a key role in the pathology of inflammation (5–13). The present consensus is emerging that both positive (inducing) and negative (inhibiting) regulation of apoptosis of tissue cells influence the initiation and the progression of tissue damage (14–17). It has been indicated that apoptosis at the inflammatory sites seems to be induced by: 1) inflammatory cytokines produced by the infiltrating hematopoietic cells as well as the tissue epithelium cells (18–20) and 2) interaction of CD95 (also called Fas) on the tissue cells and CD95 ligand (CD95L) predominantly expressed on infiltrating T-lymphocytes (21–27). In particular, the prevention of endotoxin-induced hepatitis by the defect of CD95/CD95L ligation strongly implies that CD95-mediated apoptosis of hepatocytes is the initial event in the process of hepatitis (21). In addition to apoptosis of tissue cells, apoptosis regulation of infiltrating cells also seems to influence the progression of inflammation. This indication was recently drawn by the observation of non-obese diabetic mice, a mouse model of human autoimmune diabetes (type I diabetes), under CD95-deficient conditions, which were free from destruction of insulin-producing pancreatic b cells by the infiltrating T-lymphocytes. In these mice, a defect of CD95 appeared to decrease apoptotic death of T-lymphocytes infiltrating into the pancreatic Langerhans islets, resulting in the prevention of tissue damage (28, 29). Thus, the regulation of both target tissue cells and infiltrating cells influence the progression of inflammatory diseases.

However, we are essentially ignorant of the negative (inhibitory) regulation of apoptosis at the inflammatory sites, although apoptosis must be regulated both positively and negatively, and the balance of these two regulations may critically influence the inflammation progression. This is mainly because the extracellular ligands produced at the inflammatory sites that mediate inhibitory signals for apoptosis have not been well defined so far despite the recent identification of many intracellular apoptosis inhibitory elements (14–17).

We recently isolated a novel murine apoptosis inhibitory factor, termed AIM, which is exclusively secreted by tissue macrophages including Kupffer cells in the liver (30, 31). AIM inhibits apoptosis triggered by multiple stimuli including irradiation, glucocorticoid, and CD95-cross-linking (30). At the inflammatory sites of most tissues, the macrophage is one of the cell types that is observed from the very early stage of inflammation (32–36). Hence it is possible that AIM might play a role in the negative regulation of apoptosis of cells at the inflammatory sites.

In this report, we applied a mouse hepatitis model to address potential involvement of AIM in the progression of inflammation in vivo. In addition, we present a new AIM function associated with inflammation, enhancement of the phagocytic func-
unction of macrophages, and discuss the multifunctional character of AIM.

EXPERIMENTAL PROCEDURES

Mice—Mice were bred and maintained in a specific pathogen-free animal facility at the Basel Institute for Immunology (Basel, Switzerland) and a semi-specific pathogen-free animal facility at the Tokyo Women’s Medical University (Tokyo, Japan). All animal experiments were approved by the Animal Ethics Committee of the Tokyo Women’s Medical University.

Generation of Transgenic Mice—AIM cDNA was subcloned into the pCAGGS expression vector (37). After the removal of the vector sequence, a purified DNA fragment was microinjected into fertilized eggs of C57BL/6 × DBA/2F1 mice. Embryos were transferred into the oviducts of CD-1 foster mothers. Founders were screened for transgene by PCR, and the resulting transgenic founders were bred with C57BL/6 (B6) mice to generate progenies. Transgene-positive progenies were back-crossed to B6 mice. After six back-crosses, transgene-positive and -negative littermates were used for experiments.

Induction of Endotoxin-induced Fulminant Hepatitis—Mice were immunized by 1 mg/mouse of heat-inactivated Propionibacterium acnes (Van Kampen Group, Inc., Utah) in 200 μl of phosphate-buffered saline by intravenous injection. 7 days after the immunization, each mouse was challenged by intravenous injection of 2.5 μg of lipopolysaccharide (LPS) in 150 μl of phosphate-buffered saline (38). At various time points after the LPS injection, mice were sacrificed, and blood and liver specimens were collected to evaluate liver damage.

In Situ mRNA Analysis and Histology—The liver specimens were fixed in 10% formalin and embedded in paraffin. 4-μm sections were cut and placed on silane-coated slides. These sections were subjected to in situ hybridization using digoxigenin-labeled (Roche Molecular Biochemicals) antisense-AIM cDNA probe (Ref. 30 and references therein). As a negative control, RNaseA (100 μg/ml) pretreatment was carried out before hybridization. After hybridization, sections were treated with antidigoxigenin-alkaline phosphatase, and then signals were developed by 4-nitro blue tetrazolium chloride (NTB) treatment.

The fixed liver tissues were also used for histological analysis of macrophage detection. Sections were stained with BM-8 antibody (BMA Biochemicals), which recognizes pan-macrophages/macrophages including the Kupffer cells in the liver.

Phagocytosis Assay—1.5 × 106 of either RAW264 cells (a mouse macrophage cell line (39), provided by RIKEN Cell Bank, Tsukuba, Japan) or mouse peritoneal macrophage cells derived from thioglycollate-stimulated C57BL/6 mice (30) were cultured for 2 h with appropriate numbers (cell:beads ratio was 25:1, according to the Ref. 41) of fluorescein isothiocyanate-labeled polystyrene latex beads (~1.95 μm in diameter; Sigma) in the presence or absence of recombinant AIM (rAIM). Culture supernatant of the AIM-transfected Chinese ovarian carcinoma cells was used as a source of rAIM (30, 31). As a control, culture supernatant of nontransfected Chinese ovarian carcinoma cells was used.

The fixed liver tissues were also used for histological analysis of macrophage detection. Sections were stained with BM-8 antibody (BMA Biochemicals), which recognizes pan-macrophages/macrophages including the Kupffer cells in the liver.

RESULTS

Induction of Hepatitis Strongly Up-regulated AIM Expression within Macrophage/Kupffer Cells in the Liver—Although AIM is exclusively expressed by tissue macrophages, only part of the macrophages in the tissue express AIM, suggesting the requirement of a specific microenvironment surrounding the macrophages for AIM expression induction (30). The precise mechanism for AIM expression regulation is, however, entirely unknown. In the previous report, we demonstrated that AIM was strongly expressed within infiltrating macrophages within Bacillus Calmette Guérin-induced granulomas, which may suggest potential up-regulation of AIM expression in response to inflammatory stimuli (30). To test this possibility, we introduced the endotoxin-induced hepatitis in C57BL/6 (B6) mice by immunizing mice with P. acnes followed by LPS injection (38) and analyzed AIM expression in both resident macrophages (Kupffer cells) and infiltrating macrophages. Two hours after the LPS injection, although there was no obvious increase of BM-8-positive cells (compare Fig. 1, a and c), most of these cells revealed AIM expression when assessed by in situ mRNA analysis (Fig. 1d). This was also confirmed quantitatively by a Northern blot analysis for AIM expression by using RNA from the liver of either before or 2 h-after hepatitis induction (Fig. 1f). Thus, hepatitis induction rapidly up-regulated AIM expression in Kupffer cells. A markedly increased number of BM-8-positive cells was observed in the liver after 12 h, representing massive infiltration of macrophages into the liver (Fig. 1e). Most of these cells also expressed AIM strongly (Fig. 1f). These results support the idea that inflammatory stimuli rapidly induce AIM expression in macrophages.

Increased Number of Infiltrating Macrophages in Response to Hepatitis Induction in AIM-transgenic Mice—Rapid up-regulation of AIM expression by hepatitis induction provokes a potential involvement of AIM in hepatitis pathogenesis, either via inhibition of apoptosis or another unknown function. In particular, since macrophages show a remarkable binding capacity for AIM (Ref. 30, and see Fig. 5b this report), AIM may function on macrophages at hepatitis regions in an autocrine fashion. To obtain a clue for the possible role of AIM at inflammatory sites, we generated transgenic mice overexpressing AIM under the

![Diagram](https://via.placeholder.com/150)
control of chicken β-actin promoter and cytomegalovirus enhancer (37). These mices overexpress AIM ubiquitously, resulting in a strikingly increased level of AIM concentration in the serum (Fig. 2b).

Despite the high AIM level in the serum, spontaneous infiltration of macrophages was not obvious, judging by the comparable numbers of BM-8-positive cells in the liver of non-stimulated transgenic and negative littermate mice (Fig. 3, a and b). This was also the case in all other tissues, as assessed by a histological analysis (data not shown). Thus AIM doesn’t appear to be involved in either chemotaxis or migration induction of cells in vivo. However, in response to hepatitis induction via endotoxin, transgenic mice apparently harbored an increased number of infiltrating macrophages in the liver than did control littermate mice (Fig. 3, c and d). In addition, many focal accumulations of macrophages were observed in the liver of transgenic mice. This accumulation was found at regions where the destruction of the liver tissue was apparent, harboring marked infiltration of lymphocytes and neutrophils (Fig. 3e). Although these accumulations of inflammatory cells were also found in control littermate mouse liver, the size and the number of them were remarkably larger in transgenic mice.

At inflammatory sites, macrophages are exposed to many cytokines that mediate apoptosis (18–20). Hence in AIM-transgenic mice, high doses of AIM may support survival of macrophages at inflammatory sites by inhibiting apoptosis triggered by these cytokines, resulting in seemingly increased number of infiltrating macrophages.

It is well known that CD95 (Fas)-mediated apoptosis of hepatocytes (liver cells) is an essential event of hepatitis (21). It is not likely, however, that AIM also protects hepatocytes against apoptosis, because the binding of AIM to primary hepatocytes is not obvious so far as tested by a binding study using labeled recombinant AIM (data not shown). In line with this, there was no apparent histological difference in the destruction of hepatocytes, in hepatitis-induced transgenic and negative littermate mice (data not shown). Thus AIM appears to be associated with hepatitis by supporting macrophage survival at inflammatory sites via apoptosis inhibitory effect, which may contribute to efficient clearance of dead cells and infectious or toxic reagents by macrophages. However, in certain tissues, AIM might be involved in regulating inflammation progression not only by supporting macrophage survival but also by preventing apoptosis of tissue cells.

The precise mechanism of AIM-mediated apoptosis inhibition is not clear yet. As we described in the previous reports, there was no significant difference in the expression levels of various apoptosis-inducing or -inhibiting elements, including c-FLIP, in thymocytes of AIM−/− and AIM+/− mice, as well as in a macrophage-cell line, J774.A1, in the presence or absence of recombinant AIM (30), suggesting that AIM appears to inhibit apoptosis of cells not simply by modulating the expression of these known apoptosis-related molecules but by mediating an independent signaling cascade.

**AIM Enhances Phagocytic Function of Macrophages—**

When analyzed histologically in a higher magnification, macrophages harbored small nuclei within the cells that probably represent nuclei from phagocytosed cells. Interestingly, a significantly larger number of macrophages harbored these small nuclei in AIM-transgenic mice than in negative littermate mice. In addition, the number of these small nuclei per macrophage was apparently larger in transgenic mice (Fig. 4). Thus AIM may activate the phagocytic function of macrophages.

To test this hypothesis, we determined whether AIM enhances phagocytosis by macrophages in vitro by using rAIM produced by AIM-transfected Chinese ovarian carcinoma cells (30). Either peritoneal macrophages or a macrophage-derived cell line, RAW264, both of which have binding capacity of AIM (see Fig. 5b), were incubated with fluorescein isothiocyanate-labeled polystyrene latex beads in the presence or absence of rAIM and then the number of phagocytosed beads in each cell was analyzed by a fluorocytometry (40). Fig. 5a shows the histogram of fluorescein isothiocyanate intensity from peritoneal macrophages that were incubated either in the presence

---

2 I. Haruta, C. Minjares, and T. Miyazaki, unpublished results.
FIG. 4. Enhanced phagocytosis by macrophages in AIM-transgenic mouse liver. Liver sections from AIM transgenic mouse (a) and negative littermate mouse (b and c) 8 h after hepatitis induction were stained for BM-8 and analyzed in a high magnification (×400). A number of BM-8-positive cells, which contained more than two small nuclei derived from dead cells, were detected in transgenic mouse liver (a). In contrast, BM-8-positive cells in negative littermate mouse contained 0 or 1 small nucleus derived from dead cells (b and c).

(solid line) or absence (dotted line) of rAIM. There are several peaks, which represent the number of phagocytized beads in each cell. The first peak (P0) corresponds to the macrophages that had no bead. This population was far smaller in size when macrophages were incubated in the presence of rAIM (2.9% in rAIM (+) versus 13.3% in rAIM (−)), indicating most of macrophages incubated with rAIM phagocytized beads in 2 h. In the absence of rAIM, 27.1% of macrophages phagocytized a single bead (P1), 26.1% phagocytized two beads (P2), and 14.9% phagocytized three beads (P3), respectively. These seemed to be a few macrophages that had more than four beads (P4), although they did not generate obvious peaks. In contrast, the major peak was P4, when cells were incubated in the presence of rAIM; 69% of cells had more than four beads (P4 in Fig. 5A).

Similar results were obtained when assessed by using a macrophage-derived cell line, RAW264. Almost twice the number of cells achieved phagocytosis of beads in 2 h when incubated with rAIM (60% of incubated cells in rAIM (+) versus 34% of incubated cells in rAIM (−)). Furthermore, the average of the intensity of FL-1-positive population was significantly higher in the rAIM+ population (rAIM(+)rAIM(−) = 42:29), indicating each cell phagocytized larger number of beads in the presence of rAIM.

All together AIM apparently enhances the phagocytotic function of macrophages. However, rAIM revealed more efficient enhancement in peritoneal macrophages than in RAW264 cells. This is, perhaps, due to the difference of the binding capacity for AIM between the two cell types as shown in Fig. 5B, which clearly shows the significantly higher binding capacity of peritoneal macrophages.

DISCUSSION

Inflammatory Stimuli Up-regulate AIM Expression in Macrophages—As we previously reported (30), AIM expression regulation harbors several unique characteristics. 1) AIM expression is restricted in tissue macrophages, 2) in a tissue, AIM expression is observed in only a part of the macrophages, (3) when ex vivo macrophages are cultured on a plastic dish, AIM expression entirely disappears, (4) AIM expression in macrophages is unable to be induced in vitro by any reagents that are known to activate macrophages, including phorbol 12-myristate 13-acetate, LPS, and various cytokines. These previous observations implied that a specific microenvironment is required for AIM expression induction in macrophages (30).

In the present study, we found that inflammatory stimuli appear to induce AIM expression in vivo. Soon after hepatitis induction, most of resident macrophages (Kupffer cells) and infiltrating macrophages in the liver revealed strong expression of AIM. Since AIM expression had already been up-regulated in Kupffer cells before infiltration of leukocytes was apparent, inflammatory cytokines produced by the liver tissue cells as well as by Kupffer cells themselves might predominantly induce AIM expression at the early stage of inflammation. At the later stage of inflammation, cytokines produced by infiltrating lymphocytes may also contribute to the up-regulation of AIM expression. Nevertheless, since AIM expression in ex vivo macrophages is not induced on a plastic dish in vitro even by various inflammatory cytokines (30), inflammatory stimuli may synergize the basic mechanism of AIM expression induction, which may depend on microenvironment, e.g., cell-cell interaction between specific type of cells and macrophages. Further study will precisely clarify the elements required for AIM expression induction.
AIM Enhances Phagocytosis of Macrophages; Multifunctional Character of AIM—We recently reported that AIM induces strong and sustained growth inhibition of B-lymphocytes in combination with TGF-β1 (31). Thus, other than apoptosis inhibitory effect, AIM has different functions depending on the target cell type and the combination with other cytokine(s). In line with this, we identified that AIM enhances phagocytic function of macrophages. Contrary to the case of B-lymphocytes (31), AIM revealed two different functions on macrophages, apoptosis inhibition and enhancement of phagocytosis, without specific conditions. This multifunctional character of AIM is reminiscent of various cytokines such as interleukin-4, which activates B-lymphocyte proliferation in combination of IgM cross-linking as well as induces immunoglobulin class switching toward IgE (41).

So far, a variety of reagents is known to activate phagocytic function of macrophages, including cytokines also secreted from macrophages, such as granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, and interleukin-4 and -10 (42, 43). One might argue that enhancement of phagocytosis may be an indirect effect; AIM might induce production of such cytokines in macrophages, resulting in enhanced phagocytosis. It is, however, unlikely because we could not detect any up-regulation of expression of these cytokines in macrophages by AIM in vitro,3 although we cannot mutually exclude a possibility that AIM may induce an unknown factor(s) that may enhance phagocytosis.

Perspective—It may be worth emphasizing that the unique characteristics of AIM that we presented in this report strongly imply the association of AIM with hepatitis in a sequential manner. First, AIM expression is up-regulated in response to inflammatory stimuli, and then, in an autocrine fashion, AIM supports the survival of infiltrating macrophages as well as activates phagocytosis by macrophages, which may result in an efficient clearance of dead cells and infectious or toxic reagents.

Acknowledgments—We thank Dr. Sumiko Yamakawa and Itto Okamoto Foundation for financial support, Dr. Shin Ohnishi (Tokyo, Japan) for discussions. The Basel Institute for Immunology was founded and supported by Hoffmann-La Roche Ltd, Basel Switzerland.

REFERENCES

1. Minden, A., Lin, A., McMahon, M., Lange-Carter, C., Derijard, B., Davis, R. J., Johnson, G. L., and Kan, M. (1994) Science 266, 1719–1723.
2. Pombo, C. M., Bonventre, J. V., Avruch, J., Woodgett, J. R., Kyriakis, J. M., and Force, T. (1994) J. Biol. Chem. 269, 26546–26551.
3. Westwick, J. K., Bielawa, A. E., Dbaibo, G., Hannun, Y. A., and Brenner, D. A. (1995) J. Biol. Chem. 270, 22689–22692.
4. Verheij, M., Bose, K., Lin, X. H., Yao, B., Jarvis, W. D., Grant, S., Birrer, M. J., Szabo, E., Zan, L. I., Kyriakis, J. M., Haimovitz-Friedman, A., Poku, Z., and Kolesnick, R. N. (1996) Nature 380, 75–79.
5. Steller, H. (1995) Science 267, 1445–1449.

3. C. Minjares, S-I. Yusa, and T. Miyazaki, manuscript in preparation.

6. Jacobson, M. D., Weil, M., and Raff, M. C. (1997) Cell 88, 347–354.
7. Raff, M. C. (1992) Nature 356, 397–400.
8. Vaux, D. L., Haecker, G., and Strasser, A. (1994) Cell 76, 777–779.
9. Thompson, C. B. (1995) Science 267, 1456–1462.
10. Cory, S. (1995) Annu. Rev. Immunol. 13, 513–543.
11. Yang, E., and Korsmeyer, S. J. (1996) Blood 88, 386–401.
12. Strasser, A., Huang, D. C., and Vaux, D. L. (1997) Biochim. Biophys. Acta 1333, 151–178.
13. Chao, D. T., and Korsmeyer, S. J. (1998) Annu. Rev. Immunol. 16, 395–419.
14. Reed, J. (1995) Curr. Opin. Oncol. 7, 541–546.
15. Rothstein, T. L. (1996) Curr. Opin. Immunol. 8, 362–371.
16. Nishina, H., Fischer, K. D., Radhany, L., Shalhinian, A., Hakem, R., Rubie, E. A., Bernstein, A., Mak, T. W., Woodgett, J. R., and Penninger, J. M. (1997) Nature 385, 350–353.
17. Irmler, M., Thome, M., Hahne, M., Schneider, P., Hofmann, K., Steiner, V., Bodmer, J. L., Schrotter, M., Burns, K., Mattmann, C., Rimoldi, D., French, L. E., and Tschopp, J. (1997) Nature 388, 180–185.
18. Benoist, C., and Mathis, D. (1997) Cell 89, 1–3.
19. Andre, I., Gonzalez, A., Wang, B., Katz, J., Benoist, C., and Mathis, D. (1996) Proc. Natl. Acad. Sci. U. S. A. 93, 2260–2263.
20. Wang, B., Gonzalez, A., Benoist, C., and Mathis, D. (1996) Eur. J. Immunol. 26, 1762–1769.
21. Kondo, T., Suda, T., Fukuyama, H., Adachi, M., and Nagata, S. (1997) Nat. Med. 3, 409–413.
22. Liu, W., Tan, Z., Zhang, Z., Fan, X., and Ouyang, K. (2000) Chung-Hua Kao Tsong P’eng T’ao Chih. 8, 269–271.
23. Hahn, C. S., Cho, Y. G., Kang, B. S., Lester, I. M., and Hahn, Y. S. (2000) Virology 276, 127–137.
24. Taya, N., Terimoto, Y., Shindo, M., Hirai, K., Hasebe, C., and Kohgo, Y. (2000) Br. J. Haematol. 10, 89–97.
25. Cripe, J. L., Fan, T. Klugek, F., Mehal, W. Z., and Metz, D. P. (2000) Immunol. Rev. 174, 47–62.
26. Ogawa, S., Sakaguchi, K., Takaki, A., Shiraga, K., Sawayama, T., Mour, H., Miyashita, M., Koide, N., and Tsuji, T. (2000) J. Gastroenterol. Hepatol. 15, 69–75.
27. Ji, W., Wang, H., and Feng, C. (1999) Chung-Hua Kao Tsong P’eng T’ao Chih. 7, 77–79.
28. Kim, Y. H., Kim, S., Kim, K. A., Yagita, H., Kayagaki, N., Kim, K. W., and Lee, M. S. (1999) Eur. J. Immunol. 29, 455–465.
29. Kim, S., Kim, K. A., Hwang, D. Y., Lee, T. H., Kayagaki, N., Yagita, H., and Lee, M. S. (2000) J. Immunol. 15, 2931–2936.
30. Miyazaki, T., Hirokami, Y., Matsuhashi, N., Takatsuka, H., and Naito, M. (1999) J. Exp. Med. 189, 413–422.
31. Yusa, S., Ohnishi, S., Onodera, T., and Miyazaki, T. (1999) Eur. J. Immunol. 29, 1086–1093.
32. Papaccio, G., De Luca, B., and Pisanti, F. A. (1998) J. Cell. Biochem. 71, 479–490.
33. Yoon, J. W., and Jun, H. S. (1999) Arch. Pharmacol. Res. 22, 437–447.
34. Jun, H. S., Santamarina, P., Lim, H. W., Zhang, M. L., and Yoon, J. W. (1999) Diabetes 48, 34–42.
35. Rosmalen, J. G., Martin, T., Dobbs, C., Voerman, J. S., Drexhage, H. A., Haskins, K., and Leenen, P. J. (2000) Lab. Invest. 80, 23–30.
36. Hasegawa, A., and Yodome, T. (1992) J. Biochem. (Tokyo) 112, 616–623.
37. Kayagaki, M., Ishizawa, S., Odake, H., Shimoda, F., Nakagawa, H., Mizukoshi, K., Kurashige, Y., and Koizumi, F. (1988) Acta Oto-Laryngol. Suppl. 454, 108–112.
38. Cioffi, N. L., Lehman, D. A., and Rothman, P. (1999) Adv. Immunol. 54, 229–270.
39. Dziakowski, F., Oldak, E., and Janiak, M. K. (1999) Postepy Hig. Med. Dosw. 53, 75–86.
40. Smith, M. E., van der Maesen, K., and Somera, F. P. (1998) J. Neurosci. Res. 54, 68–78.
Association of AIM, a Novel Apoptosis Inhibitory Factor, with Hepatitis via Supporting Macrophage Survival and Enhancing Phagocytotic Function of Macrophages

Ikuko Haruta, Yoichiro Kato, Etsuko Hashimoto, Christina Minjares, Shawna Kennedy, Hirofumi Uto, Katsumi Yamauchi, Makio Kobayashi, Sei-ichi Yusa, Urs Müller, Naoaki Hayashi and Toru Miyazaki

J. Biol. Chem. 2001, 276:22910-22914.
doi: 10.1074/jbc.M100324200 originally published online April 9, 2001

Access the most updated version of this article at doi: 10.1074/jbc.M100324200

Alerts:
- When this article is cited
- When a correction for this article is posted

Click here to choose from all of JBC's e-mail alerts

This article cites 43 references, 11 of which can be accessed free at http://www.jbc.org/content/276/25/22910.full.html#ref-list-1