Expert Review of Clinical Immunology

ISSN: 1744-666X (Print) 1744-8409 (Online) Journal homepage: informahealthcare.com/journals/ierm20

Soluble human major histocompatibility class I antigens: new immunomodulatory functions for old molecules

Francesco Puppo, Paola Contini, Massimo Ghio & Francesco Indiveri

To cite this article: Francesco Puppo, Paola Contini, Massimo Ghio & Francesco Indiveri (2006) Soluble human major histocompatibility class I antigens: new immunomodulatory functions for old molecules, Expert Review of Clinical Immunology, 2:1, 5-7, DOI: 10.1586/1744666X.2.1.5

To link to this article: https://doi.org/10.1586/1744666X.2.1.5

Published online: 10 Jan 2014.

Submit your article to this journal

Article views: 267

View related articles

Full Terms & Conditions of access and use can be found at
https://informahealthcare.com/action/journalInformation?journalCode=ierm20

For reprint orders, please contact reprints@future-drugs.com

Francesco Puppo, Paola Contini, Massimo Ghio and Francesco Indiveri†
†Author for correspondence
Department of Internal Medicine (DIMI), Viale Benedetto XV, n. 6, 16132 Genoa, Italy
frindi@unige.it

Soluble human major histocompatibility class I antigens: new immunomodulatory functions for old molecules

Apoptosis induced by Fas/FasL interactions plays a crucial role for the establishment of antigen-specific T-cell tolerance, both during intrathymic-negative selection and adult life

Expert Rev. Clin. Immunol. 2(1), 5–7 (2006)

The human major histocompatibility complex encodes two sets of Class I molecules, which have been termed Class Ia (or classical) and Class Ib (or nonclassical) molecules. The Class Ia molecules include the gene products of human leukocyte antigen (HLA)-A, -B and -C loci, and are characterized by broad tissue expression and by a high degree of polymorphism. The Class Ib molecules include the gene products of HLA-E, -F and -G loci and are characterized by a restricted tissue distribution and limited polymorphism.

Besides being expressed on nucleated cells, Class Ia and Ib HLA molecules are present in serum in soluble form (sHLA-I) [1,2]. The serum level of sHLA-I molecules is significantly increased in a variety of physiologic and pathologic conditions such as pregnancy, acute rejection episodes following organ allografts, acute graft-versus-host disease (GVHD) following bone marrow transplantation, autoimmune diseases, viral infections, malignant melanoma and multiple myeloma [3–8]. Due to the significant association with clinical parameters, the level of sHLA-I antigens has been suggested to represent a useful marker to predict the evolution of viral infections and to monitor the clinical course of allografts [9]. Moreover, elevated levels of functional sHLA-I molecules have been detected in blood components and might play a role in the immunomodulatory effect of autologous and allogeneic transfusions [10–13].

Several lines of evidence suggest that sHLA-I molecules are immunologically functional and may play an immunoregulatory role. In fact, they have been shown to elicit antibodies in both allogeneic and xenogeneic combinations, to inhibit the activity of alloreactive cytotoxic T lymphocytes (CTLs) [14–16], and to induce apoptosis in alloreactive and virus-specific CTLs, in activated autologous and allogeneic $CD8^+$ T cells and in $CD8^+$ natural killer (NK) cells [17–24].

There is general agreement about the mechanism underlying the inhibition of CTL activity by sHLA-I antigens. This inhibition appears to be mediated by the interactions of sHLA-I antigens α1 and -2 domains with T-cell receptors (TCRs) [14–16]. In contrast, there is conflicting information concerning the mechanism underlying induction of apoptosis of activated T cells by sHLA-I antigens. Several authors reported that sHLA-I molecules induced apoptosis of alloreactive $CD8^+$ CTLs through interaction with their TCR [17]. However, the author's data and those from other groups indicate that classical and nonclassical sHLA-I molecules trigger Fas/Fas-ligand (FasL) mediated apoptosis of

 © 2006 Future Drugs Ltd ISSN 1744-666X

phytohemoagglutinin (PHA)-activated and virus-specific $CD8^+$ T lymphocytes as well as of $CD8^+$ NK cells by interacting with the CD8 coreceptor [18–24].

Recently, the authors performed a series of experiments to clarify the intracellular mechanism(s) leading to FasL upregulation and secretion following CD8 ligation by sHLA-I molecules [25]. Results showed that sHLA-I/CD8 interaction induced the recruitment of src-like $p56^{lck}$ and syk-like ZAP-70 protein tyrosine kinases, whereas the binding of sHLA-I to the CD3/TCR complex recruited $p59^{fyn}$ PTK. Then, the engagement of CD8 by sHLA-I led to the activation of the Ca^{2+} calmodulin kinase II pathway which was eventually responsible for the NF-AT nuclear translocation. In contrast, sHLA-I/CD8 interaction, as opposed to signalling through the CD3/TCR complex, did not induce nuclear translocation of AP-1 protein complex. In addition, the authors found that the ligation of sHLA-I to CD8-recruited protein kinase C led to NF-kB activation. Both nuclear factor (NF) of activated T cells and NF-kB were responsible for the induction of FasL messenger RNA and consequently, CTL apoptosis. Moreover, FasL upregulation and CTL apoptotic death were downregulated by pharmacologically specific inhibitors of Ca^{2+}/calmodulin/calcineurin and Ca^{2+}-independent PKC signalling pathways.

Apoptosis induced by Fas/FasL interactions plays a crucial role in the establishment of antigen-specific T-cell tolerance, both during the intrathymic negative selection and adult life [26–30]. The amount of sHLA-I molecules that induces apoptosis in $CD8^+$ cells is analogous to the level found in plasma of patients with an activation of their immune system. Therefore, sHLA-I antigens secreted during immune-system activation may bind to CD8 molecules on activated $CD8^+$ T lymphocytes and NK cells and induce soluble FasL secretion. Soluble FasL may then act in an autocrine and/or paracrine fashion, triggering apoptosis in activated $CD8^+$ $CD95^+$ cells. If so, serum sHLA-I molecules may represent an important efferent arm of the network to control the expansion of $CD8^+$ cells and to downregulate immune responses and could be proposed as a potential immunosuppressive tool in the field of transplantation and autoimmunity.

References

1 Van Rood JJ, van Leeuwen A, van Santen MCT. Anti HL-A2 inhibitor in normal human serum. *Nature* 226, 366–367 (1970).

2 Charlton RK, Zmijewski CM. Soluble HL-A7 antigen: localization in the β-lipoprotein fraction of human serum. *Science* 170, 636–637 (1970).

3 Puppo F, Brenci S, Lanza L *et al.* Increased level of serum HLA Class I antigens in HIV infection. Correlation with disease progression. *Hum. Immunol.* 40, 259–266 (1994).

4 Puppo F, Scudeletti M, Indiveri F, Ferrone S. Serum HLA Class I antigens: markers and modulators of an immune response? *Immunol. Today* 16, 124–127 (1995).

5 Hunt JS, Jadhav L, Chu W, Geraghty DE, Ober C. Soluble HLA-G circulates in maternal blood during pregnancy. *Am. J. Obstet. Gynecol.* 183, 682–688 (2000).

6 Ugurel S, Rebmann V, Ferrone S, Tilgen W, Grosse-Wilde H, Reinhold U. Soluble human leukocyte antigen-G serum level is elevated in melanoma patients and is further increased by interferon-α immunotherapy. *Cancer* 92, 369–376 (2001).

7 Wiendl H, Feger U, Mittelbronn M *et al.* Expression of the immune-tolerogenic major histocompatibility molecule HLA-G in multiple sclerosis: implications for CNS immunity. *Brain* 128, 2689–2704 (2005).

8 Leleu X, Le Friec G, Facon T *et al.* on behalf of the Intergroupe Francophone du Myelome. Total soluble HLA class I and soluble HLA-G in multiple myeloma and monoclonal gammopathy of undetermined significance. *Clin. Cancer Res.* 11, 7297–7303 (2005).

9 Puppo F, Indiveri F, Scudeletti M, Ferrone S. Soluble HLA antigens: new roles and uses. *Immunol. Today* 18, 154–155 (1997).

10 Ghio M, Contini P, Mazzei C *et al.* Soluble HLA class I, HLA class II and Fas ligand in blood components: a possible key to explain the immunomodulatory effects of allogeneic blood transfusions. *Blood* 93, 1770–1777 (1999).

11 Ghio M, Contini P, Mazzei C *et al.* Soluble HLA class I and Fas ligand molecules in blood components and their role in the immunomodulatory effects of blood transfusions. *Leuk. Lymphoma* 37, 1–8 (2000).

12 Puppo F, Ghio M, Contini P, Mazzei C, Indiveri F. Fas, Fas ligand, and transfusion immunomodulation. *Transfusion* 41, 416–418 (2001).

13 Ghio M, Contini P, Mazzei C *et al. In vitro* immunosuppressive activity of soluble HLA Class I and Fas ligand molecules: do they play a role in autologous blood transfusion? *Transfusion* 41, 988–996 (2001).

14 Hausmann R, Zavazava N, Steinmann J, Müller-Ruchholtz W. Interaction of papain digested HLA class I molecules with human alloreactive cytotoxic T lymphocytes (CTL). *Clin. Exp. Immunol.* 91, 183–188 (1993).

15 Parham P, Clayberger C, Zorn SL, Ludwig DS, Schoolnik GK, Krensky AM. Inhibition of alloreactive cytotoxic T lymphocytes by peptides from the α2 domain of HLA-A2. *Nature* 325, 625–628 (1987).

16 Dal Porto J, Johansen TE, Catipovic B. A soluble divalent Class I major histocompatibility complex molecule inhibits alloreactive T cells at nanomolar concentrations. *Proc. Natl Acad. Sci. USA* 90, 6671–6675 (1993).

17 Zavazava N, Krönke M. Soluble HLA class I molecules induce apoptosis in alloreactive cytotoxic T lymphocytes. *Nature Med.* 2, 1005–1010 (1996).

18 Contini P, Ghio M, Merlo A *et al.* Soluble HLA class I/CD8 ligation triggers apoptosis in EBV-specific $CD8^+$ cytotoxic T lymphocytes by Fas/Fas-ligand interaction. *Hum. Immunol.* 61, 1347–1351 (2000).

19 Gansuvd B, Haghiara M, Munkhbat B *et al.* Inhibition of Epstein-Barr virus (EBV)-specific $CD8^+$ cytotoxic T lymphocyte (CTL) activity by soluble HLA class I *in vitro*. *Clin. Exp. Immunol.* 119, 107–114 (2000).

20 Puppo F, Contini P, Ghio M *et al.* Soluble human MHC class I molecules induce soluble Fas ligand secretion and trigger apoptosis in activated $CD8^+$ $Fas(CD95)^+$ T lymphocytes. *Int. Immunol.* 12, 195–203 (2000).

21 Spaggiari GM, Contini P, Carosio R *et al.* Soluble HLA class I molecules induce Natural Killer cell apoptosis through the engagement of CD8. Evidence for a negative regulation exerted by CD94/NKG2A complex and KIR2D. *Blood* 99, 1706–1714 (2002).

22 Spaggiari GM, Contini P, Dondero A *et al.* Soluble HLA Class I induces NK cell apoptosis upon the engagement of killer activating HLA class I receptors through FasL/Fas interaction. *Blood* 100, 4098–4107 (2002).

23 Fournel S, Aguerre-Girr M, Huc X *et al.* Soluble HLA-G1 triggers CD95/CD95 ligand-mediated apoptosis in activated CD8+ cells by interaction with CD8. *J. Immunol.* 164, 6100–6104 (2000).

24 Contini P, Ghio M, Poggi A *et al.* Soluble HLA-A,-B,-C and -G molecules induce apoptosis in T and NK CD8+ cells and inhibit cytotoxic T cell activity through CD8 ligation. Eur. *J. Immunol.* 33, 125–134 (2003).

25 Contini P, Ghio M, Merlo M, Poggi A, Indiveri F, Puppo F. Apoptosis of antigen-specific T lymphocytes upon the engagement of CD8 by soluble HLA Class I molecules is Fas Ligand/Fas mediated: evidence for the involvement of p56lck, calcium calmodulin kinase II, and calcium-independent protein kinase C signaling pathways and for. NF-κB and NF-AT nuclear translocation. *J. Immunol.* 175, 7244–7254 (2005).

26 Mountz JD, Zhou T, Wu J, Wang W, Su X, Cheng J. Regulation of apoptosis in immune cells. *J. Clin. Immunol.* 15, 1–16 (1995).

27 van Parijs L, Abbas AK. Role of Fas-mediated cell death in the regulation of immune responses. *Curr. Opin. Immunol.* 8, 355–361 (1996).

28 Yonehara S, Nishimura Y, Kishil S *et al.* Involvement of apoptosis antigen Fas in clonal deletion of human thymocytes. *Int. Immunol.* 6, 1849–1856 (1994).

29 Lynch DH, Ramsdell F, Alderson MR. Fas and FasL in the homeostatic regulation of immune responses. *Immunol. Today* 16, 569–574 (1995).

30 Kurts C, Heath WR, Kosaka H, Miller JFAP, Carbone F. The peripheral deletion of autoreactive $CD8^+$ T cells induced by cross-presentation of self-antigens involves signaling through CD95 (Fas, Apo-1). *J. Exp. Med.* 188, 415–420 (1998).

Affiliations

- ***Francesco Puppo***
Department of Internal Medicine (DIMI), Viale Benedetto XV, n. 6, 16132 Genoa, Italy
- ***Paola Contini***
Department of Internal Medicine (DIMI), Viale Benedetto XV, n. 6, 16132 Genoa, Italy
- ***Massimo Ghio***
Department of Internal Medicine (DIMI), Viale Benedetto XV, n. 6, 16132 Genoa, Italy
- ***Francesco Indiveri***
Department of Internal Medicine (DIMI), Viale Benedetto XV, n. 6, 16132 Genoa, Italy
frindi@unige.it: