Regulation of Major Histocompatibility Gene Expression in Human Vascular Smooth Muscle Cells

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Human atheromata, but not normal blood vessels, contain numerous smooth muscle cells (SMC) that bear class II major histocompatibility (MHC) antigens. These lesions also contain leukocytes that can secrete cytokines, which may modulate SMC functions. Because of morphologic evidence for immune-activated (class II+) SMC in vascular lesions, we studied the regulation by cytokines of MHC gene expression in SMC cultured from human vessels. Under basal conditions, these SMC contained mRNA for class I MHC (detected by Northern blotting with a cDNA probe for HLA-B7) and expressed surface class I MHC product determined by enzymelinked immunosassay with monoclonal antibody (MAb) W6/32. Unstimulated SMC contained little or no class II MHC mRNA (probed with HLA-DR alpha cDNA) or surface antigen (examined using MAb I2). Secretory products of activated human leukocytes (the cell-free supernatant of a mixed leukocyte reaction) induced class II MHC antigen expression by SMC after 3 days. Treatment of SMC with interferon (IFN)-alpha or -beta (1000 U/ml for 72 hours) increased class I MHC mRNA content and surface antigen but did not alter class II expression. Immune IFN (IFN-gamma), a leukocyte product known to induce class II MHC expression in classical antigen-presenting cells as well as epithelial and endothelial cells, not only increased class I MHC expression by SMC but also induced substantial levels of class II MHC mRNA and surface antigen. IFN-gamma (ED50 -- 10 U/ml) increased class II MHC mRNA maximally after 2 to 3 days and surface expression linearly from 1 to 4 days. Immunohistochemical study demonstrated few class II+ SMC in cultured human SMC under basal conditions but homogeneous expression of high levels of DR antigen after exposure to IFN-gamma for 3 days. Neither interleukin-1 (IL-1 alpha or beta), tumor necrosis factor alpha (TNF), nor endotoxin altered class II expression by SMC. Local secretion of IFN-gamma by activated leukocytes may account for the presence of HLA-DR+ SMC in the human atheroma. Immune activation of SMC might participate in the pathogenesis of vasculitis and arteriosclerosis, particularly in the form found in the coronary arteries of transplanted hearts.


Recent studies of cells found in human atherosclerotic plaques have identified smooth muscle cells (SMC), some of which exhibit class II major histocompatibility (MHC) antigens.1-4 Most nucleated cells bear class I MHC determinants, but the finding of class II antigens on these cells was unexpected. MHC determinants are highly polymorphic cell surface glycoproteins that play a key role in recognition of foreign tissues and in antigen presentation to immunocompetent cells.5,6 The traditional view considered only cells derived from bone marrow (including lymphocytes, mononuclear phagocytes, and Langerhans' and dendritic cells) to be capable of expressing class II MHC determinants, hence their common designation as human leukocyte antigens (HLA). It is now known that a variety of nonleukocytic cell types, although they ordinarly lack class II antigens, can synthesize these molecules under some conditions. For example, human vascular endothelial cells and fibroblasts and thyroid epithelial and neural cells can express such determinants after exposure to the cytokine immune or gamma interferon (IFN-gamma).7-12 In addition to SMC, human atheromata contain a considerable number of T-lymphocytes and macrophages.2,4,13 When activated, both of these cell types can elaborate a variety of cytokines including interleukins, tumor necrosis factors, or IFN-gamma.14 Morphologic studies have established that the human atherosclerotic plaque contains HLA DR+ SMC adjacent to such cytokine-producing cells. To learn more about the mechanisms that may mediate this unusual behavior of SMC in atheromata, we have examined the control of MHC gene expression by products of activated leukocytes as well as by defined recombinant cytokines in characterized cultures of human vascular SMC. Inducible expression of class II histocompatibility antigens by these vessel wall cells may be of significance in the pathogenesis of arteriosclerosis, in various vasculitides, and in allograft rejection.
Methods

Cytokines

Recombinant human IFN-γ was provided by Genentech, Incorporated (South San Francisco, CA), recombinant human leukocyte IFN-α A was supplied by Peter Sorter of Hoffman-LaRoche (Nutley, NJ), and natural human IFN-β was purchased from Lee Biomolecular Research, Incorporated (San Diego, CA). Recombinant human interleukin-1α (IL-1α) was supplied by Peter Lemedico of Hoffman-LaRoche and recombinant interleukin-1β (IL-1β) by Charles A. Dinarello of Tufts University (Boston, MA). Recombinant human interleukin-6 (IL-6), also known as β2 interferon, hepatic stimulating factor, or B cell stimulatory factor-2, was obtained from Genzyme, Incorporated (Boston, MA). Recombinant human tumor necrosis factor α (TNFα) was provided by Michael Palladino of Genentech, Incorporated.

Antibodies

Human class I histocompatibility antigens were detected using monoclonal antibody W6/32 (IgG 2a). A hybridoma cell line expressing this antibody was supplied by Mark I. Green of the University of Pennsylvania (Philadelphia, PA). The IgG was isolated from hybridoma supernatants by protein-A affinity chromatography. Class II histocompatibility antigens were detected using monoclonal antibody I-2 (IgG 2a), supplied as mouse ascites fluid by Lee Nadler and Stuart F. Schlossman of the Dana-Farber Cancer Institute (Boston, MA). A mouse IgG2a κ myeloma protein (UPC 10, Sigma Chemical Company, St. Louis, MO) was used as a type- and class-matched irrelevant antibody for control purposes. Jan Vilcek of New York University (New York, NY) provided bovine antihuman IFN-β antiserum. Rabbit antinatural human IFN-γ was purchased from Interferon Sciences, Inc. (New Brunswick, NJ).

Nucleic Acid Probes

Class I HLA mRNA was detected using a 1.8-kilobase (kb) probe derived by Bgl II cleavage of a genomic clone of HLA B7 cDNA. Messenger RNA for class II antigens was detected with a 550 bp Pst I fragment of DB10 probe for HLA DRα. Beta-tubulin transcripts were detected with a 1.05-kb Bam HI to Pst I fragment of RβT 3, a gift of Stephen R. Farmer of Boston University, Boston, Massachusetts.

Cell Cultures

Human vascular SMC were prepared from explants of unused portions of saphenous veins obtained at the time of coronary artery bypass surgery. This use of normally discarded human tissues was approved by the Human Investigation Review Committee of New England Medical Center (Boston, MA). Aortic SMC were isolated enzymatically from the inner third of the tunica media of tissue obtained from organ donors, with the cooperation of the New England Organ Bank. The adventitia and abluminal two thirds of the tunica media were removed before dissociation of the tissue with collagenase. These cells were prepared, characterized, and cultured in Dulbecco’s modified Eagle’s (DME) medium containing fetal bovine serum (10%) with HEPES (25 mM). All components of tissue culture media were tested for endotoxin contamination using the chromogenic Limulus amebocyte lysate assay. Only media that contained a final concentration of endotoxin less than 40 pg/ml were used for these studies to avoid stimulation of endogenous cytokine production by the endotoxin-sensitive SMC. These cells exhibited the typical morphologic characteristics of vascular smooth muscle in vitro, including a pattern of growth in hills and valleys. Even after several passages in culture, many of these cells stained with HHF-35, a monoclonal antibody that selectively recognizes muscle-specific forms of actin and that does not react with endothelial cells or fibroblasts.

Human peripheral blood mononuclear cells (PBMC) for mixed leukocyte reactions were prepared from venous blood obtained with informed consent from three healthy unrelated male adult donors. The blood was anticoagulated with heparin (100 U/ml), and PBMC were isolated by centrifugation over Ficoll-Hypaque (400 g, 30 minutes, 20°C). The interface cells were washed with phosphate-buffered saline (PBS) and resuspended at 4.5x10⁶ cells/ml in DME supplemented with fetal calf serum (FCS) (10%). The cells from the three donors were mixed and incubated at 37°C for 4 days. At the end of this period, the cells were sedimented by centrifugation, and the supernatants were equilibrated with DME by repeated centrifugation by using a Centricon-10 device (Amicon, Bedford, MA). They were stored at −70°C.

RNA Extraction and Nucleic Acid Hybridization

RNA was isolated from cultured SMC by phenol extraction after lysis in guanidinium isothiocyanate. After electrophoresis on agarose gels (1.2%) that contained formaldehyde (2.2 M), the RNA was transferred to nylon membranes (Hybond-N, Amersham Company, Arlington Heights, IL). DNA probes were labeled by nick translation or by random hexanucleotide priming by using 32P-labeled nucleotide triphosphates. Prehybridization, hybridization, and autoradiography were done with standard techniques.

Measurement of Cell Surface Antigen Level by Enzyme-linked Immunosorbent Assay

SMC were cultured in 96-well plates for study by cell-based enzyme-linked immunosorbent assay (ELISA). After treatment with the test stimulus, the cell layers were washed with PBS containing bovine serum albumin (BSA, 10 mg/ml) to block nonspecific binding sites. The wells were incubated with various dilutions of the test antibody or buffer alone for 2 hours at 4°C. The cell layers were then washed three times with PBS-BSA, then incubated for 1 hour with horse antimouse IgG antibody conjugated with biotin (Vector Laboratories, Burlingame, CA) diluted 1:1000. After an additional wash in PBS-BSA, the cell layers were incubated for 30 minutes with streptavidin-alkaline phosphatase diluted 1:1000 (Zymed Laboratories, South San Francisco, CA). After this incubation, the cell layers were washed three more times with PBS-BSA and finally, with PBS alone. The cell-associated enzyme activity was then measured by incubation for 15 to 30 minutes with paranitrophenyl phosphate (1 mg/ml) in diethanolamine (0.1 M, pH 10.3) that contained levi-
sole (1 mM, Sigma Chemical Company) to block endogenous phosphatase activity. The reaction was stopped by addition of two volumes of sodium hydroxide (2 M), and the absorbance at 410 nm was read in an automated microplate photometer. Control incubations performed with equivalent dilutions of the irrelevant type- and class-matched antibody (UPC-10) run with most experiments yielded negligible absorbance.

**Immunohistochemical Evaluation of Major Histocompatibility Antigen Expression**

SMC were cultured in Labtek 4-well chambers (Miles Laboratories, Naperville, IL). After treatment with the test stimulus, the cell layers were fixed with acetone at 4°C for 20 seconds and were evaluated by immunohistochemical studies with selective antibodies by using standard avidin-biotin immunoperoxidase techniques. Cell layers were washed with PBS that contained horse serum (1%) for 10 minutes. Then, monoclonal antibody obtained as mouse ascites fluid or IgG fraction was diluted 1:100 in PBS and incubated with the cell layers for 1 hour at ambient temperature. After washing with PBS, biotinylated horse antihorse IgG was applied for 40 minutes. The slides were again washed and incubated for 30 minutes with vectastain ABC reagent, a mixture of avidin and biotinylated horseradish peroxidase (Vector Laboratories, Burlingame, CA). The slides were washed again and developed in peroxidase substrate solution (50 ml acetate buffer (0.1 M, pH 5.0) that contained 25 μl of a 30% hydrogen peroxide solution and aminoethylcarbazole (10 mg dissolved in 2.5 ml N,N-dimethylformamide). The controls in all immunohistochemical experiments included the omission of primary antibody and parallel reactions with panels of cells of known positive or negative reactivity.

**Results**

**Secretory Products of Activated Human Leukocytes Induce Surface Expression of Major Histocompatibility Antigens on Smooth Muscle Cells**

Human venous and arterial SMC expressed little or no class II MHC antigens under basal conditions in culture (Figure 1) in accord with the in situ observations of Jonasson et al. We tested whether products of activated leukocytes could induce class II MHC expression by SMC and might thus account for the finding of HLA DR+ SMC in the vicinity of T-lymphocytes in the complicated atheromatous plaque. We exposed SMC for 72 hours to the recombinant human IFN species tested significantly augmented class I MHC mRNA levels to a greater extent than the other IFNs tested (Figure 2A). Although each of the recombinant human IFN species tested significantly increased the surface expression of class I antigen determined quantitatively by ELISA (Figure 3), the magnitude of this increase was substantially less than the increase in the corresponding steady-state mRNA level. Inspection of SMC layers exposed to IFN-γ and stained immunohistochemically for class I antigens showed no striking difference (data not shown), consistent with the modest changes in surface expression of these determinants documented by quantitative ELISA.

Exposure of SMC to IFN-α or IFN-γ caused accumulation of class I HLA mRNA within 24 hours and produced maximal increases after 48 hours (Figure 4, middle row). Each of the IFN species tested increased the surface expression of class I antigens maximally after 24 to 48 hours.

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**Figure 1.** Mixed leukocyte reaction supernatants induce surface expression of class II HLA in venous and aortic smooth muscle cells. Cells derived from saphenous vein or aorta were incubated for 3 days with a mixed leukocyte reaction supernatant prepared as described in text. Surface expression of class II MHC antigen was measured with monoclonal antibody 12 as described. Data are mean absorbance ±SD, n=6. MLR = mixed leukocyte reaction.
Figure 2. Interferons modulate the expression of histocompatibility genes in human vascular smooth muscle cells (SMC). Cultures of human saphenous vein SMC were incubated under usual culture conditions (medium), or in the presence of recombinant human IFN-α, -β, or -γ (1000 U/ml) for 72 hours. In the case of IFN-β, replicate cultures were incubated with an antibody to human IFN-β (anti-IFN-β) or nonimmune serum (FCS). RNA was separated electrophoretically and transferred to nylon membranes. The position of migration of the 28S and 18S ribosomal subunits are indicated by arrowheads on this and subsequent Northern blots. A. A hybridization with a class I major histocompatibility antigen probe. B. Hybridization of the same membrane with a probe for class II HLA derived from a HLA-DRα cDNA clone. The blot was stripped and rehybridized with a probe for a constitutively expressed form of β-tubulin (lower panel) to confirm the integrity of the RNA, and that approximately equal amounts of RNA were loaded in each lane.

Class II Human Leukocyte Antigen Expression

Although all cultures of SMC tested express class I MHC genes under basal conditions, we found little or no class II MHC mRNA in unstimulated SMC examined by using an HLA-DR probe that encodes well-conserved α chain sequences (Figure 2B). The surfaces of untreated SMC contained only low levels of immunoreactive class II MHC antigen measured by ELISA with monoclonal antibody 12 (Figures 1, 7, 8, and 9). Only occasional discrete cells in cultured monolayers of human SMC reacted with anticlass II antibody as detected by immunohistochemical staining (Figure 5A, arrowheads).

One product of activated leukocytes likely to mediate the induction of class II molecules on SMC by MLR supernatants is IFN-γ. We tested the effect of purified human IFN-γ made by recombinant DNA technology on this function of SMC. Incubation with this IFN-γ caused marked accumulation of class II MHC mRNA by SMC (Figures 2B and 4). Immune IFN induced accumulation of this mRNA after 24 hours of exposure and produced maximal levels after 48 hours of treatment (Figure 4, right hand panel). These increases in class II mRNA corresponded to induced surface expression of antigens reactive with anti-HLA-DR antibody (Figures 6, 7, 8, and 9). Recombinant IFN-γ (1000 U/ml for 72 hours) induced expression of class II MHC antigens on the surface of aortic, as well as venous, SMC determined by ELISA, an effect inhibited by anti-IFN-γ antibody (Figure 6). Immunohistochemical study demonstrated homogeneous induc-
Interferons increase the expression of class I major histocompatibility (MHC) antigen on the surface of human vascular smooth muscle cells (SMC). Cultures of human saphenous vein SMC were incubated with the indicated cytokine for 72 hours. The concentration of Interferons α, β, and γ was 1000 U/ml. IL-6 (IFN-β3) was included at 100 ng/ml. The expression of class I MHC antigen on the surface of the cultured cells was measured by enzyme-linked immunosorbent assay. Values obtained in parallel incubations with a type- and class-matched irrelevant antibody (UPC-10) were all less than 0.011 absorbance units and were subtracted from the data shown. Data plotted are the means ± SD of three observations. Compared to incubation without cytokine by Student’s t test, the increases produced by interferons α, β, and γ were significant (p=0.004), but IL-6 produced no significant effect (p>0.08).

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Discussion
Application of modern tools of morphologic analysis to human atherosclerotic lesions has confirmed the presence of smooth muscle cells and macrophages, long suspected on the basis of conventional microscopic observations and extrapolations from animal experiments. However, the presence of numerous T-lymphocytes and class II MHC-bearing SMC in the advanced human atheroma was unexpected. Up to 20% of the cells in the “shoulder” portion of human carotid endarterectomy specimens are T-lymphocytes. Uncomplicated “fatty streaks” in the aortas of young trauma victims also contain T-cells. The necrotic cores of advanced human atheroma abound with cells which react with monoclonal antibodies that recognize mononuclear phagocytes. The SMC that bear class II HLA markers are found in the vicinity of these infiltrating leukocytes in atheroma, but SMC in uninvolved arterial tissue seldom exhibit these antigens. These various findings indicate activation of the immune system in the human atherosclerotic lesion.

Traditionally, only cells derived from bone marrow were thought capable of expressing class II MHC antigens. It is now clear that vascular endothelial cells, certain epithelial cells, cells in the central nervous system, and even human fibroblasts can express class II MHC molecules in an inducible manner. Immune IFN, also known as IFN-γ, is thought to be the physiologic inducer of class II expression on classical antigen presenting cells such as the monocyte/macrophage. Since the human atheroma contains leukocytes capable of IFN-γ secretion, this cytokine may be a pathophysiologically relevant modulator of class II antigen expression in the vessel wall as well. Indeed, the supernatant from a human mixed leukocyte reaction, which contains the secretory products of activated mononuclear cells, induced surface expression of class II MHC antigens on SMC (Figure 1). This study used defined cultures of human vascular SMC and a panel of human cytokines to explore the regulation of MHC gene expression in these cells.

As expected, SMC expressed class I antigens constitutively, although all of the interferons tested (with the exception of IL-6, also known as β2-interferon) caused modest increases in class I MHC mRNA and surface antigen. Other experiments indicated that the cytokines IL-1 and TNF may actually suppress class I surface expression in these cells (data not shown). In contrast, IFN-γ markedly increased the expression of class II genes in SMC. In the absence of this cytokine, only rare cells in SMC cultured without added stimuli reacted with anticlass II MHC antibodies (Figure 5A). Exposure to IFN-γ, even at low concentrations (10 U/ml), provoked substantial accumulation of class II MHC mRNA and induced the expression of class II MHC antigen on the surface of the treated cells. Immunohistochemical study showed that IFN-γ caused uniform appearance of class II antigen, indicating that all SMC in these cultures responded as a homogeneous population to this cytokine (Figure 5). These various data support a strong effect of IFN-γ on the transcription of class II MHC genes and the synthesis and surface expression of class II gene products by human vascular SMC.

The ability of SMC to express class II MHC genes in an inducible manner has several important implications for the pathogenesis of vascular diseases. The surface class II MHC product is required for accessory function in antigen presentation. Only cells that bear these determinants can efficiently present antigen to helper T-cells or be recognized as foreign by these cells. Even when induced to express class II MHC antigens, SMC or...
fibroblasts appear less effective in stimulating an allogeneic immune response in vitro than are endothelial cells obtained from the same human donor. Fibroblasts also appear less immunogenic than endothelial cells, although both cell types bear class II antigens. Nonetheless, evidence from murine models of vasculitis suggest the
importance of SMC expression of class II antigens in vascular pathology. Hart and colleagues have shown that autologous lymphocytes sensitized against syngeneic SMC in vitro can produce a granulomatous vasculitis when reinjected into syngeneic recipient mice. SMC cultured from the aortas of MRL/lpr mice that develop spontaneous autoimmune vasculitis express class II MHC antigens. Rodent SMC can also express immunoreactive Ia protein.

Infiltration of the vessel wall by mononuclear leukocytes characterizes vasculitic lesions in animals and many human vascular diseases. These leukocytes are a likely source for IFN-γ that could trigger class II MHC gene expression in human SMC in vivo. The signal for recruitment of the mononuclear cells to foci of vascular inflammation or injury may depend on local production of chemoattractants. Blood vessel wall cells themselves may provide this initial stimulus, since human vascular smooth muscle and endothelial cells can secrete IL-1, a chemotactic factor for a variety of leukocytes. Further synthesis of chemoattractant inflammatory mediators by the recruited leukocytes could amplify, sustain, or propagate the local inflammatory response.

The present findings on MHC gene regulation in SMC, taken together with recent immunohistochemical studies from other laboratories, suggest possible mechanisms for ongoing immune activation in chronic human atherosclerosis. Our observation that human SMC appear to require IFN-γ to express Class II MHC genes suggests that mononuclear leukocytes found in the plaque are in an activated state that is associated with production of this cytokine. This conclusion implies, in turn, that human atheromata probably contain cytokines such as interleukins, since activated mononuclear phagocytes release these substances and because the usual pathway for T-cell activation involves such co-stimulatory mediators.

It is as yet undetermined whether this immune activation is antigen-specific and might play a primary or causative role in atherogenesis, or whether the leukocytes are latecomers to the lesion, responding to nonantigen specific mediators including endogenous vascular IL-1. In this regard, it is of interest that early arterial intimal le-
Figure 6. IFN-γ induces class II major histocompatibility (MHC) antigen expression in aortic smooth muscle cells (SMC). Aortic SMC were incubated for 3 days with medium alone (control), IFN-γ (1000 U/ml) with or without polyclonal rabbit antiserum to IFN-γ, or IFN-β (1000 U/ml), or bacterial lipopolysaccharide (10 μg/ml). Surface expression of class II HLA antigen was measured by enzyme-linked immunosorbent assay with monoclonal antibody 12 as described in Methods. Data are mean absorbance ± SD, n=6.

Figure 7. Selectivity of the ability of immune interferon to induce class II HLA expression on the surface of human vascular smooth muscle cells (SMC). Cultures of human saphenous vein SMC were incubated in usual culture medium (control) or with the indicated cytokine for 72 hours. The concentration of IL-α and -β was 10 ng/ml. The concentration of TNF was 20 ng/ml. The concentration of IFN-α or -γ was 1000 U/ml. The expression of class II major histocompatibility (MHC) antigen on the cell surfaces was measured as described in the legend to Figure 6. Data shown are mean ± SD, n=8.

Figure 8. Immune interferon produces time-dependent increases in the expression of class II major histocompatibility (MHC) antigen on the surface of human vascular smooth muscle cells (SMC). Cultures of human saphenous vein SMC were exposed to IFN-γ (1000 U/ml) for the indicated time periods. Class II MHC expression was measured by the enzyme-linked immunosorbent assay technique with monoclonal antibody I2. Data shown are mean ± SD, n=8.

Figure 9. Immune interferon increases class II major histocompatibility (MHC) antigen expression on the surface of human vascular smooth muscle cells (SMC) in a concentration-dependent manner. Human saphenous vein SMC cultures were treated with IFN-γ at the indicated concentrations for 72 hours. Measurement of class II antigen expression and data presentation are as described in the legend to Figure 6. Data shown are mean ± SD, n=6.

Allogeneic class II MHC antigens as foreign. Therefore, the ability of SMC to express class II MHC genes may contribute to both the afferent and the effector limbs of the cellular immune response to SMC in the monocyte media of transplanted coronary arteries. This accelerated arteriosclerosis in the coronaries of allografted hearts is currently a major limitation in clinical cardiac transplantation. Further studies of the mechanism of interactions between leukocyte products and human vascular cells will doubtless continue to provide new insights into the pathogenesis of this and other human vascular diseases and may eventually suggest new therapies.

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