Experimental Abdominal Aortic Aneurysm Formation Is Mediated by IL-17 and Attenuated by Mesenchymal Stem Cell Treatment

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Background—Abdominal aortic aneurysm (AAA) formation is characterized by inflammation, smooth muscle activation and matrix degradation. This study tests the hypothesis that CD4+ T-cell–produced IL-17 modulates inflammation and smooth muscle cell activation, leading to the pathogenesis of AAA and that human mesenchymal stem cell (MSC) treatment can attenuate IL-17 production and AAA formation.

Methods and Results—Human aortic tissue demonstrated a significant increase in IL-17 and IL-23 expression in AAA patients compared with control subjects as analyzed by RT-PCR and ELISA. AAA formation was assessed in C57BL/6 (wild-type; WT), IL-23−/− or IL-17−/− mice using an elastase-perfusion model. Heat-inactivated elastase was used as control. On days 3, 7, and 14 after perfusion, abdominal aorta diameter was measured by video micrometry, and aortic tissue was analyzed for cytokines, cell counts, and IL-17–producing CD4+ T cells. Aortic diameter and cytokine production (MCP-1, RANTES, KC, TNF-α, MIP-1α, and IFN-γ) was significantly attenuated in elastase-perfused IL-17−/− and IL-23−/− mice compared with WT mice on day 14. Cellular infiltration (especially IL-17–producing CD4+ T cells) was significantly attenuated in elastase-perfused IL-17−/− mice compared with WT mice on day 14. Primary aortic smooth muscle cells were significantly activated by elastase or IL-17 treatment. Furthermore, MSC treatment significantly attenuated AAA formation and IL-17 production in elastase-perfused WT mice.

Conclusions—These results demonstrate that CD4+ T-cell–produced IL-17 plays a critical role in promoting inflammation during AAA formation and that immunomodulation of IL-17 by MSCs can offer protection against AAA formation. (Circulation. 2012;126[suppl 1]:S38–S45.)

Key Words: abdominal aortic aneurysm ■ interleukins ■ inflammation ■ stem cells ■ lymphocytes

Abdominal aortic aneurysm (AAA) formation involves chronic inflammation, upregulation of proteolytic pathways, oxidative stress, and loss of arterial wall matrix. The critical inflammatory pathways that lead to smooth muscle cell activation and apoptosis during AAA formation remain to be elucidated. Previous studies have postulated an important role for proinflammatory cytokines in various mouse models of AAA. However, the specific role of cytokines in the modulation of inflammation, oxidative stress, smooth muscle apoptosis, and vascular remodeling remains to be defined. IL-17, a key T-cell–produced proinflammatory cytokine, is known to be an important regulator of inflammation and apoptosis in chronic inflammation. Previous studies have also demonstrated a predominance of CD4+ T cells in AAA. However, the contribution, cellular sources, and signaling pathways of CD4+ T cells and IL-17 remain unknown. Thus, the present study investigates the hypothesis that CD4+ T-cell–produced IL-17 modulates inflammation and smooth muscle cell activation in the pathogenesis of AAA. Human aortic tissue from AAA patients, a murine elastase-perfusion AAA model, and in vitro studies were used to test this hypothesis.

Recent studies have raised the possibility of stem cell therapies for improving the outcome of inflammation-based diseases including aortic aneurysms. Mesenchymal stem cells (MSCs) are multipotent with the capability to differentiate into a wide range of cell types. Another fundamental property of MSCs is the immunosuppressive activities, which

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are postulated to have tremendous potential to translate to novel therapeutic strategies for tissue repair and immunomodulation.14,15 Therefore, in the pursuit of pharmacological modalities for AAA, the immunomodulatory effects of MSCs on the pathogenesis of AAA was investigated in the murine elastase-perfusion AAA model.

Methods

Human Aortic Tissue Analysis
Collection of human aortic tissue was approved by the University of Virginia’s Institutional Review Board (protocol No. 13178). Preoperative consent was obtained from all patients. AAA tissue from male patients was resected during open surgical AAA repair, and abdominal aortic tissue was obtained from transplant donor patients to serve as control subjects. Tissue was homogenized in Trizol, and RNA was purified per manufacturer’s protocol (Qiagen, Valencia, CA). cDNA was synthesized using the iScript cDNA Synthesis Kit (BioRad, Hercules, CA). Quantitative (real-time) RT-PCR was performed with primer sets (MGW/Operon, Huntsville, AL) in conjunction with SsoFast EvaGreen Supermix (BioRad, Hercules, CA). Primers used were as follows: GAPDH forward, CATT- GTGGAAGGCTCATGA; GAPDH reverse, TCTTCTGGGTGGCACTGATG; IL-23p19 forward, GAGCAGCAACCCTGAGTGGAAGGGCTCATGA; IL-17A reverse, CAAATTTCCTTCCATCATTA; IL-17 forward, ATGACTCCTGGGAAGACCTCATGG; IL-17 reverse, TTAGGCCCACCATGGTGACAC. Gene expression was calculated by using the relative quantification method (Average reference gene), where GAPDH was used as the reference gene.

Animals
All animal experimentation was approved by the University of Virginia’s Institutional Animal Care and Use Committee. Male C57BL/6, IL-17A−/− and IL-23−/− mice (8–12 weeks of age) were used. C57BL/6 mice were obtained from Jackson Laboratories (Bar Harbor, ME). IL-17A−/− and IL-23−/− (p19 subunit knockout) mice, which were back-crossed onto C57BL/6 background for 10 generations, were obtained from Dr Yoichiro Iwakura (The Institute of Medical Sciences, University of Tokyo) and Genentech (San Francisco, CA), respectively.

Elastase Perfusion Model of Aneurysm Formation
A murine elastase perfusion model of AAA formation was used as previously described.16,17 Briefly, the infrarenal abdominal aorta was isolated in situ before perfusion, after perfusion, and before harvesting the aorta for histology and immunohistochemistry. AAA specimens were immediately fixed in 10% formalin. After fixation, tissues were dehydrated in ascending concentrations of ethanol and embedded in paraffin. Sections were prepared for immunohistochemical analysis.

Enzyme-Linked Immunosorbent Spot Assay
Primary CD4+ T cells were purified from mouse aortic tissue using a magnetic bead-based cell isolation kit (Miltenyi Biotec, Auburn, CA). An IL-17A enzyme-linked immunosorbent spot (ELISPOT) assay (R&D Systems, Minneapolis, MN) was used as instructed by the manufacturer. Spot-forming cells were counted under a microscope. Results are presented as the average number of spot-forming cells per total number of cells plated.

Cytokine Measurements
Cytokine content in aortic tissue (human and mice) homogenates was quantified using the Bioplex Bead Array technique using a multiplex cytokine panel assay (Bio-Rad Laboratories, Hercules, CA).

Purification of Primary Aortic Smooth Muscle Cells
Primary aortic smooth muscle cells were purified from C57BL/6 mice as previously described.18

Flow Cytometry
Aortic tissue from mice was minced and incubated for 15 minutes at 37°C with collagenase type IA (Sigma) in PBS with 0.5% BSA and 2 mmol/L EDTA. The cell suspension was prepared for flow cytometry analysis for cell counts using Counting Beads (Invitrogen), as previously described.19 Cells were blocked with anti-mouse CD16/CD32 (1 μg/mL; eBioscience) before surface labeling with the following antibodies: Aqua (2 μg/mL; Invitrogen), APC-Cy7–labeled CD45 (eBioscience), FITC–labeled B220, APC-labeled CD4, Pacific blue–labeled CD8, PerCP Cy5.5–labeled CD11b, PE-labeled Ly6-G, PE–Texas Red–labeled NK1.1, and PE-Cy7–labeled CD11c (all BD Biosciences). FACS data were analyzed using FlowJo software 8.8.

Human Placental Mesenchymal Stem Cell Isolation
Mesenchymal stem cells (MSCs) were isolated from the chorionic villi of term human placenta as previously described.20 Further characterization of MSCs done by flow cytometry confirms a pattern consistent with MSC population showing an expression of CD90, CD73, CD105, CD29, and CD44 (Michael P. Murphy, MD; unpublished data, 2011). MSCs lacked expression of CD45, CD34, CD14, CD19, and HLA-DR. Immunofluorescence staining of embryonic stem cell antigens in MSCs demonstrated the expression of Oct-4, Nanog, SSEA-3, and SSEA-4. After isolation and subsequent culture, early-passage placental MSCs were plated in a 96-well plate at a density of 15,000 cells per designated well for the in vitro assays. Also, 1×10^6 MSCs were injected into WT mice via tail vein injection on day 1 in the in vivo experiments.

Mixed Lymphocyte Reactions
The mononuclear cell (MNC) fraction of peripheral blood specimens from healthy volunteers was separated using Ficoll-Paque PLUS separation (GE Healthcare Bio-Sciences AB, Piscataway, NJ). In vitro experiments of mixed lymphocyte reactions using MNCs (3×10⁶) and MSCs were performed wherein MNCs were stimulated with mouse anti-human CD3 (1 μg/mL; BD Biosciences, San Diego, CA) and mouse anti-human CD28 (0.5 μg/mL; BD Biosciences). Cell cultures were then incubated for 6 days at 37°C/5% CO₂. Eighteen hours before the end of the experiment, 1H-thymidine (0.5 μCi/well) was added to each of the wells. On day 7, cell proliferation was determined by measuring the incorporation of 1H-thymidine using a β-plate reader and quantified as counts per minute (cpm). Cell culture supernatants were analyzed for IL-17A by an ELISA (R & D Systems).

Histology and Immunohistochemistry
AAA specimens were immediately fixed in 10% formalin. After 24 hours, fixed samples were embedded in paraffin, and sections were stained by immunohistochemistry. Aortic sections were also stained with hematoxylin and eosin and Verhoeff-Van Gieson for elastic fiber. Further characterization of MSCs done by flow cytometry confirms a pattern consistent with MSC population showing an expression of CD90, CD73, CD105, CD29, and CD44 (Michael P. Murphy, MD; unpublished data, 2011). MSCs lacked expression of CD45, CD34, CD14, CD19, and HLA-DR. Immunofluorescence staining of embryonic stem cell antigens in MSCs demonstrated the expression of Oct-4, Nanog, SSEA-3, and SSEA-4. After isolation and subsequent culture, early-passage placental MSCs were plated in a 96-well plate at a density of 15,000 cells per designated well for the in vitro assays. Also, 1×10^6 MSCs were injected into WT mice via tail vein injection on day 1 in the in vivo experiments.
After incubation with an avidin-biotin complex, immuno-reactivity was visualized by incubating the sections with 3,3-diaminobenzidine tetrahydrochloride (DAKO Corp, Carpinteria, CA) to produce a brown precipitate. Sections were then counterstained with hematoxylin. For smooth muscle α-actin (SM-α) staining, the alkaline phosphatase-conjugated monoclonal anti–SM-α antibody (Sigma, St Louis, MO) was used. Images were acquired using 20 magnification by an Olympus microscope equipped with an Olympus digital camera, and ImagePro software.

Results

IL-23 and IL-17 Expression Is Increased in Human AAA

Gene expression of IL-17 and IL-23 was significantly increased in aortic tissue from AAA patients compared with control subjects (1.9±0.23-fold and 1.6±0.13-fold, respectively) (Figure 1). Protein levels of IL-17 (37.8±3.8 versus 6.0±3.2 pg/mL) and IL-23 (182.5±21.0 versus 21.6±6.0 pg/mL) were significantly elevated in aortic tissue from AAA patients compared with control subjects (Figure 2). A significant increase in the protein levels of RANTES, MCP-1, IL-8, TNF-α, MIP-1α, and IFN-γ was also observed in aortic tissue from AAA patients compared with control subjects (Figure 2).

IL-23 and IL-17 Modulates Inflammation and Contributes to AAA Formation

With the use of the elastase perfusion model, aortic diameter was measured in WT, IL-17−/−, and IL-23−/− mice (Figure 3A and 3B). There was no significant difference in aortic diameter between elastase-perfused and heat-inactivated elastase-perfused (control) WT mice on days 3 and 7 (Figure 3C). However, AAA formation in WT mice after elastase perfusion was a consistent finding on day 14 with a mean aortic diameter increase of 141.1±16.1% versus 51.1±4.1% (elastase-perfused versus control WT mice, respectively) (Figure 3C). Importantly, AAA formation was significantly attenuated in elastase-perfused IL-17−/− (89.4±7.4%) and IL-23−/− (88.5±13.8%) mice compared with elastase-perfused WT mice (141.1±16.1%) on day 14, although not completely decreased to WT control levels (Figure 3D). There was no significant difference in aortic diameter between control and elastase-perfused IL-17−/− and IL-23−/− mice compared with corresponding WT mice on days 3 and 7 (data not shown).

A significant increase in IL-17, IL-23, IFN-γ, RANTES, KC, MIP-1α, TNF-α, and MCP-1 expression was observed in
aortic tissue from elastase-perfused WT mice compared with control subjects on day 14 (Figure 4). More importantly, proinflammatory cytokines were significantly attenuated in aortic tissue from elastase-perfused IL-17−/− and IL-23−/− mice compared with elastase-perfused WT mice (Figure 4). IL-23 expression was not significantly decreased in IL-17−/− mice compared with elastase-perfused WT mice (Figure 4). A significant increase in IL-17 and IL-23 production in CD4+ T cells from aortic tissue of WT mice after elastase perfusion compared with controls on days 3, 7, and 14 (Figure 5D). Furthermore, comparative histology and immunostaining of aortic tissue revealed a significant attenuation of inflammatory cell (CD3+ T cells, macrophages, and neutrophils) infiltration, increase in smooth muscle α-actin expression, and decrease in elastic fiber

Figure 3. Abdominal aortic aneurysm (AAA) formation is attenuated in IL-17−/− and IL-23−/− mice. A, Infrarenal mouse aortas were perfused with elastase (0.4 U/mL) or heat-inactivated elastase (control), and aortic diameter was measured on days 3, 7, and 14. The abdominal aorta (day 0, first panel, represented by white arrows) was significantly increased in diameter after elastase-perfusion of wild-type (WT) mice (day 14, last panel, represented by black arrows). B, A representative AAA dissected from an elastase-perfused WT mouse on day 14. C, Elastase-perfused WT mice had no significant change in aortic diameters on days 3 and 7 compared with controls. On day 14, aortic diameter was significantly increased in elastase-perfused WT mice compared with controls. D, A significant decrease in aortic diameter occurred in elastase-perfused IL-17−/− and IL-23−/− mice compared with elastase-perfused WT mice. n=6 to 9 animals/group; *P<0.05 versus corresponding controls; #P<0.05 versus elastase-perfused WT mice.

Figure 4. Proinflammatory cytokine production is attenuated in elastase-perfused IL-17−/− and IL-23−/− mice. Cytokine expression was measured on day 14 in aortic tissue from wild-type (WT), IL-17−/−, and IL-23−/− mice that underwent control or elastase perfusion. A significant increase in IL-17 and IL-23 expression occurred in elastase-perfused WT mice compared with controls. A significant attenuation of IFN-γ, RANTES, KC, MIP-1α, TNF-α, and MCP-1 occurred in elastase-perfused aortic tissue from IL-17−/− or IL-23−/− mice compared with elastase-perfused WT controls. n=6 to 9 animals/group; *P<0.05 versus WT control; #P<0.05 versus elastase-perfused WT mice.

CD4+ T Lymphocytes Play a Key Role in AAA Formation Via IL-17 Production

Cell infiltration in aortic tissue was compared between elastase-perfused and control WT mice on days 3, 7, and 14 by flow cytometry. A significant increase in CD4+ and CD8+ T cells as well as CD11c+ dendritic cells was observed in elastase-perfused WT mice compared with controls at day 3 (Figure 5A). Cellular infiltration peaked on day 7 and remained elevated on day 14 with a significant increase in T lymphocytes (CD4+ and CD8+), macrophages (CD11b+), dendritic cells (CD11c+), and neutrophils (Ly6G+) in elastase-perfused WT mice compared with controls (Figure 5B and 5C). On day 14, a significant attenuation of CD4+ and CD8+ T lymphocytes as well as neutrophils but not macrophages or dendritic cells occurred in aortic tissue from elastase-perfused IL-17−/− mice compared with elastase-perfused WT mice (Figure 5C). Furthermore, ELISPOT analysis demonstrated a significant increase in IL-17 production in CD4+ T cells from aortic tissue of WT mice after elastase perfusion compared with controls on days 3, 7, and 14 (Figure 5D). Furthermore, comparative histology and immunostaining of aortic tissue revealed a significant attenuation of inflammatory cell (CD3+ T cells, macrophages, and neutrophils) infiltration, increase in smooth muscle α-actin expression, and decrease in elastic fiber

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disruption in elastase-perfused IL-17−/− mice compared with elastase-perfused WT mice (Figure 5E).

**IL-17 Modulates Aortic Smooth Muscle Cell Activation**

One feature of the pathogenesis of AAA formation is inflammation and vascular remodeling of aortic smooth muscle cells (ASCs). To test if IL-17 can independently modulate the activation of ASCs, primary ASCs (1×10⁶ cells) were transiently (5 minutes) exposed to elastase (0.4 U/mL). Cells were washed with PBS, and fresh media was added. Cytokine measurement in culture supernatants was done after 24 hours or 48 hours. ASCs were also separately treated with recombinant IL-17 (10 ng/mL) for 24 hours or 48 hours, and cytokine production in the supernatants was measured at end points. Elastase or IL-17 treatment of ASCs significantly increased the production of IL-6, MCP-1, KC, MIP-1α, TNF-α, and RANTES (Figure 6). There was no production of either IL-17 or IL-23 from ASCs after elastase treatment (data not shown).

**Placental MSCs Suppress Lymphocyte Activation and Attenuate IL-17 Production and AAA Formation**

In vitro experiments demonstrated that activation of mononuclear cells (MNCs) by anti-human CD3 and CD28 resulted in significant cell proliferation compared with unstimulated MNCs (18,323.2±882.2 versus 1475.7±182.0 cpm, respectively) (Figure 7A). MSCs cocultured with MNCs suppressed the proliferation of activated MNCs (646.5±29.1 versus 18,323.2±882.2 cpm, respectively). Furthermore, MSCs significantly attenuated IL-17 production by activated MNCs (1874.5±103.3 pg/mL, respectively) (Figure 7B).
Based on these results, we tested the immunomodulatory effects of MSCs on AAA formation. Elastase-perfused WT mice were treated with MSCs ($1 \times 10^6$ cells; intravenously) on day 1 and aortic diameter was measured on day 14. Aortic diameter was significantly attenuated in MSC-treated mice compared with untreated elastase-perfused WT mice (82.1 ± 9.2% versus 141.1 ± 16.1%, respectively) (Figure 8A). Furthermore, aortic tissue from MSC-treated WT mice displayed a significant attenuation of proinflammatory cytokines, including IL-17, compared with elastase-perfused WT mice (Figure 8B and 8C). Also, comparative histology and immunohistological analysis of aortic tissue revealed a significant attenuation of inflammatory cell infiltration (CD3+ T cells were noted to be one of the initial cell subsets to be significantly increased in aortic tissue during AAA and remained markedly elevated on days 3, 7, and 14, which also correlated with significant IL-17 production in WT mice after elastase perfusion compared with controls. In vitro studies confirmed that elastase or IL-17 treatment modulates activation of ASMCs. Furthermore, MSC treatment of WT mice after elastase perfusion significantly attenuated AAA formation as well as proinflammatory cytokine production, including IL-17. Immunomodulation of lymphocytes by MSC treatment was confirmed by in vitro studies that demonstrated a significant reduction in IL-17 production and lymphocyte proliferation. Taken together, these results demonstrate that CD4+ T-cell–produced–IL-17 plays a critical role in inflammation, ASMC activation, and AAA formation and that mitigation of IL-17 by MSC treatment offers significant protection from AAA formation.

Recent studies demonstrate an important role for T-cell–produced IL-17 in models of chronic inflammation and leukocyte trafficking.6,7,16 IL-17 is largely produced by memory T cells and stimulates innate immunity and host defense.7 IL-17A production by T lymphocytes can be regulated by IL-23 independent of T-cell receptor activation and has been shown to be a potent mediator of neutrophil and macrophage recruitment in various chronic inflammatory models.21 Macrophages or dendritic cells are known to be prominent sources of IL-23, which has been shown to regulate CD4+ T-cell–produced IL-17 in various models.22

IL-17 has proinflammatory properties and acts on a broad range of cell types to induce the expression of various cytokines, chemokines, and metalloproteinases.7 Recent studies have shown a definitive role of IL-17 in the promotion of vascular inflammation and atherosclerosis.21,23 The current study identifies a key role of the IL-23/IL-17 axis in AAA formation by showing decreased aneurysm phenotype as well as overall reduction in proinflammatory cytokine/chemokine production in IL-23−/− and IL-17−/− mice. Although both IL-23−/− and IL-17−/− mice were significantly protected from AAA formation, the expression of IL-17 was significantly attenuated in IL-23−/− mice but not vice versa, thereby confirming the proinflammatory effector role of IL-17 in our model. Of particular interest was the significant attenuation of TNF-α, IFN-γ, and MCP-1 in elastase-perfused IL-17−/− mouse aortas. These cytokines have been shown to mediate aneurysm formation in animal studies and are upregulated in human AAA.3,4,24 The regulation of these inflammatory cytokines by IL-17 suggests that CD4+ T-cell–produced IL-17 is an early and upstream mediator of the inflammatory cascade involved in AAA.

The regulation of inflammatory cytokines and MMP suppression by MSC treatment of aortic aneurysm has been previously reported.10 The suppression of T cells, dendritic cells, and macrophages by MSCs has also been demonstrated previously.25 Based on our findings that AAA formation in our mouse model was IL-17–dependent and that MSCs suppressed both MNC proliferation and IL-17 production, we assessed the potential of MSC therapy in vivo. Here, MSC
Mesenchymal stem cells (MSCs) attenuate abdominal aortic aneurysm (AAA) formation. A, Aortic diameter measurement of elastase-perfused wild-type (WT) mice treated with MSCs showed a significant attenuation in AAA formation compared with elastase-perfused WT mice alone on day 14. B, Aortic tissue from elastase-perfused WT mice treated with MSCs showed a significant attenuation in IL-17 and IL-23 production compared with elastase-perfused WT mice alone. C, MSC treatment significantly attenuated proinflammatory cytokine/chemokine production in elastase-perfused WT mice. Comparative histology and immunohistochemistry performed on day 14 indicate that WT mice treated with MSCs have a significant decrease in CD3+ T cell, neutrophil (PMN), and macrophage (Mac-2) infiltration (arrows indicate areas of immunostaining), increase in smooth muscle cell α-actin (SM-αA) expression, as well as decrease in elastic fiber disruption (Verhoeff-Van Gieson staining for elastin), compared with elastase-perfused WT mice. n=5 to 9 mice/group; *P<0.05 versus control; #P<0.05 versus elastase.

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/content/126/17/e278.full.pdf
In the article by Sharma et al, “Experimental Abdominal Aortic Aneurysm Formation Is Mediated by IL-17 and Attenuated by Mesenchymal Stem Cell Treatment,” which was published in September 11, 2012, Supplement 1 of the journal (Circulation. 2012;126:S38–S45), Figure 8D was missing from the Figure.

The correct Figure 8 should have appeared as follows: