Accelerated Atherosclerosis in Mice Lacking Tumor Necrosis Factor Receptor p55

(Received for publication, August 1, 1996, and in revised form, August 27, 1996)

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Tumor necrosis factor-α (TNF) is produced primarily from macrophages and promotes numerous inflammatory reactions associated with atherosclerosis including the induction of vascular adhesion molecules and the recruitment and proliferation of monocyte/macrophages. There are two receptors known to elicit TNF responses, termed p55 and p75. Since p55 is thought to play the primary role in inflammatory processes, we postulated that the absence of p55 in mice would protect against atherosclerosis. In contrast, C57BL/6 mice lacking p55 had aortic sinus lesion sizes 2.3-fold larger than C57BL/6 wild type mice when fed an atherogenic diet (37,123 versus 16, 688 ± 2887 μm², respectively, p < 0.0004). Plasma lipid levels were not different between strains. A 3-fold increase in the uptake and degradation of acetylated low density lipoprotein for p55-null as compared with wild type mice was demonstrated in cultured peritoneal macrophages. Immunohistochemical staining for scavenger receptor protein in the aortic sinus was more intense in lesions from the p55-null mice as compared with wild type controls. Our results support the concept that increased scavenger receptor activity contributes to excessive fatty streak formation. We conclude that TNF p55 receptors protect against atherosclerotic lesion development in the mouse.

EXPERIMENTAL PROCEDURES

Animals and Diets—Receptor p55-null mice were generated by homologous recombination in a C57BL/6CR-derived embryonic stem cell line (20, 21). The p55-null female mice used throughout this study were maintained on a C57BL/6CR genetic background. Mice homozygous for p55-null are overtly normal under unchallenged conditions, although they display defects in resistance to intracellular pathogens and are resistant to the lethal effects of endotoxin and maintaining resistance to bacterial infection (15–17). This work, coupled to previous studies using antibodies generated against each receptor (19), suggests that the p55 receptor regulates host defense mechanisms and is a primary mediator of inflammatory processes. In contrast, the role of p75 as a signaling receptor for TNF is less well established. This receptor is associated with TNF-mediated T-cell death and induction of necrotizing skin lesions (18). Despite the wealth of information concerning TNF and its inflammatory activities, the involvement of this cytokine in atherosclerotic lesion development is incompletely understood.

To address the role of TNF receptor p55 activity in lesion development, atherosclerosis and lipid levels were quantified in mice genetically engineered to lack the p55 receptor. p55-null mice had lesion sizes 2.3-fold larger than wild type mice, yet plasma lipid levels were nearly identical between strains. The increase in lesion size in p55-null mice was accompanied by a 3-fold elevation in scavenger receptor activity as assessed in cultured peritoneal macrophages. Direct evaluation of scavenger receptor protein in aortic sinus sections from the mice suggests that this receptor is overexpressed in lesions from mice lacking the p55 receptor. Our results support the concept that TNF modulates scavenger receptor activity, and the loss of this modulation in p55-null mice contributes to accelerated fatty streak formation. We conclude that p55 contributes to protection against fatty streak lesion formation in atherosclerosis diet-fed mice.
ingston, MA) and C57BL/6CR p55null (p55-null) mice from 6–8 weeks of age were fed a pelleted rodent chow diet (Wayne Rodent BLOX 8604, Teklad Test Diets, Madison, WI) or a pelleted “atherogenic” diet containing 15% by weight fat (primarily cocoa butter), 1.25% cholesterol, and 0.5% cholic acid as described (22, 23). Mice were maintained in a temperature-controlled (25 °C) specific pathogen-free facility with a strict 12-h light/dark cycle and given free access to food and water. Mice were fed either rodent chow or the atherogenic diet for 14 weeks, fasted 4 h or overnight, and blood was collected from the retroorbital sinus into tubes containing anticoagulant (1 mM EDTA). Plasma was stored at 70 °C prior to analysis. Mice were killed using 5 mg of Nembutal/10 g body weight, the lower vena cava was severed, and mice were perfused via the left atrium with approximately 20 ml of a buffered 4% formalin solution. Hearts and aortas were treated as discussed below. This project was approved by the Animal Care and Use Committee of the University of Washington (Protocol 2140-11).

**Analytical Measurements**—Mice were fasted for 4 h, plasma lipids were quantified using commercial kits, and lipoproteins were separated as described previously (23, 24). Mice were fasted overnight and apolipoproteins were quantified using immunoblotting techniques with antibodies to specific apolipoproteins as described previously (23–25). In some cases, VLDL, LDL, and HDL were isolated from plasma for chemical analysis by sequential NaBr density ultracentrifugation (26) or nonequilibrium density gradient ultracentrifugation (27).

**Aortic Sinus Lesion Area**—Quantification of atherosclerotic fatty streak lesions was done by evaluation of lesion size in the aortic sinus as described (28, 29). Briefly, the heart and upper section of the aorta were removed from animals, cleaned of peripheral fat under a dissecting microscope, and sectioned directly under and parallel to the atrial leaflets. The upper section was incubated in 0.2 m sodium phosphate buffer (pH 7.4) containing 30% sucrose for 4–6 h, embedded in O.C.T. medium, and frozen. Every third section (10 μm thick) throughout the aortic sinus (400 μm) was taken for analysis. Sections were evaluated for fatty streak lesions following lipid staining with Oil Red O and nuclei staining with hematoxylin. Lesion areas and numbers of nuclei per section were quantified using a Compaq 286 computer (Compaq Computer, Houston, TX) equipped with an FG-100 image acquisition board, a high resolution video camera, and Sony video monitor. Area measurements were evaluated using the Optimas Image Analysis Software Package (BioScan Inc., Edmonds, WA).

**Immunohistochemistry**—For macrophage staining, slides were incubated overnight with an anti-Mac-1 antibody (No. 01711D, Pharmingen Inc., San Diego, CA; diluted 1:5) followed by a 2-h incubation with biotinylated anti-rat antibody (Catalog number BA 4001, Vector Laboratories, Inc., Burlingame, CA, diluted 1:200). Staining for iNOS was performed by incubating sections overnight with a polyclonal anti-iNOS antibody (No. N32030/L6, Transduction Laboratories, Lexington, KY; diluted 1:100) followed by a 2-h incubation with horseradish peroxidase-conjugated anti-rabbit antibody (No. 4010–05, Southern Biotechnology Associates Inc.; diluted 1:200). Smooth muscle cells were evaluated using a horseradish peroxidase-conjugated mouse monoclonal raised to human smooth muscle cell actin (No. U7033, Dako, Inc., Carpinteria, CA; diluted 1:6). Staining for scavenger receptor was performed using anti-scavenger receptor antibodies (clone 2F8, which recognizes both type I and type II murine scavenger receptors (30), kindly provided by Dr. Siamon Gordon, Oxford, UK) followed by incubation with a biotinylated secondary antibody. Binding was detected by incubating sections with horseradish peroxidase-conjugated streptavidin (1:200) followed by using the aminoethylcarbazole chromogen detection system (Dako, Inc.). All slides were counterstained with hematoxylin. Prior to immunostaining, cells were incubated with 3% hydrogen peroxide to eliminate endogenous peroxidase activity and blocked with 5% nonfat milk. No reactivity in the aortic sinus was observed when either the primary or secondary antibodies were eliminated.

**Scavenger Receptor Activity**—Control and receptor-deficient mice maintained on chow diet were killed by cervical dislocation, and the peritoneal cavities of each mouse were flushed with 5 ml of phosphate-buffered saline to collect macrophages. Cells were pelleted and resuspended in Dulbecco’s modified Eagle’s media (Sigma) containing 10% fetal bovine serum (Sigma), 100 units/ml penicillin, 100 units/ml streptomycin and supplemented with 2.0% glutamine. Cells were plated at approximately 5 × 10^6 cells per well and incubated for 48 h prior to treatment with 125I-Ac-LDL as described by Bonet et al. (31).

**Statistical Analysis**—Data are reported as mean ± S.E. The Student’s t test was used to compare independent means in most cases. Lesion area comparisons were evaluated using the Mann-Whitney test. p < 0.05 was accepted as statistically significant.

**RESULTS**

**Atherosclerotic Lesion Development**—To determine if TNF receptor p55 modulates the development of atherosclerosis in mice, p55-null mice were generated in the atherosclerosis-susceptible C57BL/6 strain. Using this strain, we can directly evaluate whether the p55-null allele increases or decreases atherosclerotic lesion formation. Female C57BL/6 and p55-null mice were fed rodent chow or the high fat/high cholesterol (atherogenic) diet for 14 weeks, and proximal aortic sinus lesion development was evaluated. Lesion size in the p55-null mice was 2.3-fold larger than that of C57BL/6 wild type mice (mean area of lesions ± S.E. was 16, 688 ± 2,887 in the wild type and 37,123 ± 3,485 for p55-null animals; p < 0.0004) (Fig. 1). Neither strain developed aortic atherosclerotic lesions when maintained on the chow diet for up to 8 months.

Despite the difference in lesion size, the cellular composition of the lesions appeared similar between wild type and p55-
deficient mice. In both strains, lesions were observed both along the aortic wall and at the valve cusps. Similar to wild type, the p55-null lesions were characterized by a lipid-enriched core with regions of reduced nuclear staining (Fig. 2, A and B). Immunochemical analysis showed that lesions consisted primarily of macrophages (Fig. 2C) with minimal or no smooth muscle cell involvement (data not shown). Macrophages were also the primary cell type seen in cellular caps covering lesioned areas. The ratio of cell nuclei number to lesion area was quantified among lesions from both strains. This ratio was 30% smaller for p55-null mice as compared with wild type mice (p < 0.003). In fact, comparing lesions of similar size between genotypes showed that p55-null mouse lesions contained less cells which suggests that either cells were more lipid enriched or lesions contained a greater proportion of extracellular lipid than in wild type animals.

As a marker of activated macrophages, we examined lesioned sections for the presence of inducible nitric-oxide synthase (iNOS). This enzyme produces nitric oxide (NO) which is involved with both bacterial killing (32) and maintenance of vasodilation (33). The expression of iNOS can be mediated by a variety of cytokines including TNF (34, 35). Macrophages examined within lesioned areas of both wild type and p55-null mice (Fig. 2D) expressed iNOS and, thus, were likely to be biologically active and responsive to their environment. iNOS was not detected in nonlesioned areas. The similarity in lesion structure between wild type and p55-null mice suggests that mechanisms for lesion development may be similar in each strain but that this process is accelerated in the p55-null mice.

**Plasma Lipoproteins**—Possible mechanisms for accelerated fatty streak formation in p55-null mice include elevations in plasma cholesterol levels above those seen for wild type mice, alterations in the chemical composition of lipoproteins, or alterations at the arterial wall directly affecting macrophage function. To address the first two mechanisms, we examined plasma lipid concentrations and plasma lipoprotein and apolipoprotein levels in wild type and p55-null mice fed the rodent chow and atherogenic diets (Table I).

Plasma cholesterol levels were elevated in both strains by the atherogenic diet, and this increase was reflected primarily in the LDL/VLDL cholesterol fraction. However, no significant differences were observed between strains fed this diet. Additionally, the ratio of HDL to total cholesterol, a measure of atherogenic risk, was similar for both strains. Using nonequilibrium density gradient ultracentrifugation by a single vertical spin to separate plasma lipoproteins from mice fed the atherogenic diet, we observed no differences in lipoprotein profiles between strains (data not shown). Finally, whereas plasma triglyceride levels were significantly reduced for both strains upon feeding the atherogenic diet, no differences were observed between strains in this parameter.

Quantification of the major apolipoproteins showed that, although the atherogenic diet induced significant changes in several components, no major differences existed between strains (Table I). To verify that plasma lipoprotein compositions were not dramatically altered between strains fed the atherogenic diet, we sequentially isolated VLDL, LDL, and HDL and determined the cholesterol and apoprotein concentrations in these fractions (data not shown). We observed no major differences between strains in these parameters. Approximately 97–99% of apoB was isolated in the VLDL/LDL fractions, whereas the majority of apoE, apoA-I, and apoA-II were isolated in the HDL fraction. 40% of the total cholesterol was isolated in the VLDL fraction, 40% in the LDL fraction, and 20% in the HDL fraction, and no significant differences were observed between strains. These observations demonstrate that loss of p55 did not alter the lipoprotein concentration or composition in mice fed the atherogenic diet.

**Scavenger Receptor Activity**—We postulated that genetic differences in atherosclerosis susceptibility between wild type and p55-null mice are mediated at the level of the artery wall. Since the accumulation of lipid by macrophages is a characteristic feature of these lesions, one potential site by which genetic factors could mediate fatty streak formation is by the increased uptake of atherogenic lipoproteins by scavenger receptors. It is thought that such receptors are responsible for macrophage foam cell formation via the uptake of modified lipoproteins (36) and are an attractive candidate for study because TNF is reported to down-regulate such activity in cultured macrophages (37). Mouse peritoneal macrophages taken from chow diet-fed wild type and p55-null mice were incubated at 37 °C with increasing concentrations of [125I]acetyl-LDL (Ac-LDL), a ligand for the scavenger receptor, and degradation of radiolabeled protein was measured (31). As shown in Fig. 3, degradation of Ac-LDL was saturable for both wild type and p55-null mice, with half-maximal values of 12 µg/ml for both mouse strains. Scatchard analysis was consistent with a 3-fold increase in the number of scavenger receptors accounting for the increased degradation seen in p55-null mice. Although these experiments were performed using peritoneal macrophages, the results support the concept that increased fatty streak formation in p55-null mice may be due, at least in part, to an increase in the number of scavenger receptors available for lipoprotein uptake in the artery wall.

**Aortic Scavenger Receptor Expression**—To determine whether altered scavenger receptor expression was altered in vivo, lesions from control and receptor-deficient mice were immunostained using the 2F8 monoclonal antibody (30) which recognizes both types I and II murine scavenger receptors (Fig. 4). Quantitative differences in staining intensity was determined using several dilutions of the antibody. Increased scavenger receptor protein expression at lesioned sites was ob-

### Table I

| Lipid or apoprotein | Chow diet | Atherogenic diet |
|---------------------|-----------|------------------|
|                     | +/+       | +/-              | +/+               | +/-               |
| Total Cholesterol (TC) | 77 ± 4 (5) | 62 ± 4 (6) | 348 ± 30 (13)** | 365 ± 33 (12)** |
| HDL-c               | 45 ± 4 (5) | 35 ± 2 (4) | 28 ± 4 (13)** | 37 ± 4 (12)** |
| LDL/VLDL-c          | 32 ± 3 (5) | 32 ± 5 (4) | 321 ± 32 (13)** | 328 ± 32 (12)** |
| Triglyceride        | 25 ± 3 (5) | 18 ± 1 (4) | 5 ± 2 (8)** | 6 ± 0.4 (9)** |
| ApoA-I              | 134 ± 12 (4) | 108 ± 6 (5) | 73 ± 6 (4)** | 91 ± 10 (5)** |
| ApoA-II             | 12 ± 3 (4) | 6 ± 1 (5) | 6 ± 2 (4) | 14 ± 4 (5) |
| ApoE                | 8 ± 1 (4) | 8 ± 1 (5) | 6 ± 1 (4) | 6 ± 1 (5) |
| ApoB-100            | 2 ± 1 (4) | 1 ± 1 (5) | 4 ± 1 (4) | 3 ± 1 (5) |
| ApoB-48             | 1.4 ± 0.4 (4) | 0.6 ± 0.1 (5) | 12 ± 2 (4)** | 11 ± 3 (5)** |

Footnote symbols denote statistical difference at *p* = 0.05–0.01 and *p* = 0.005–0.001, respectively, for mice of the same genotype fed the two diets. The Student’s *t*-test was used to determine significance between groups.
served in the p55-null mice as compared with wild type controls. Staining in nonlesioned sites was not seen in either strain suggesting that scavenger receptor expression is associated with the atherogenic process. No staining was observed when either the primary or secondary antibody was eliminated from the staining process (data not shown). These results are consistent with the increased scavenger receptor activity observed using cultured peritoneal macrophages and suggests that loss of p55 increases scavenger receptor protein expression within developing atherosclerotic lesions.

**DISCUSSION**

In this report, we tested the role of the TNF receptor p55 in atherosclerosis development in the mouse. These studies constitute the first report of atherosclerosis in mice with genetically engineered changes in cytokine receptor gene expression. At the artery wall, this receptor is thought to mediate the action of TNF in inflammatory processes, such as the activation of endothelial adhesion molecules and monocyte chemotaxis and differentiation. This receptor may also mediate processes directed by a second ligand produced by activated T-cells, lymphotixin. Thus, we hypothesized that atherosclerosis development would be reduced in mice lacking receptor function. In contrast to this, proximal aortic fatty streak lesions were 2.3-fold larger in p55-null mice compared to wild type mice, suggesting that the TNF receptor p55 plays an important role in protection against atherosclerosis.

The protective effect of p55 may occur through multiple mechanisms because of the functional pleiotropy of TNF and its receptor molecules (19). Many responses associated with the production of TNF are considered to promote atherosclerosis including the induction of leukocyte adhesion molecules (4, 5) and increased endothelial cell permeability (3). Thus, by eliminating p55, these processes should be reduced and atherosclerosis diminished. Since we observed the opposite result, it was useful to focus on evaluating potential mechanisms associated with a role for TNF in protection against lesion formation. One such mechanism would be modulation of lipoprotein metabolism by p55. Precedence exists for such action, as specific enzymes mediating lipoprotein metabolism have also been shown to be modulated by TNF (9, 40). In addition, acute TNF exposure by injection or exposure to endotoxin results in increased plasma VLDL concentrations (10). However, we observed no differences in plasma lipid, lipoprotein, or apolipoprotein levels between strains fed the atherogenic diet. Thus, differences in atherosclerosis severity between strains is clearly attributable to chronic functions of the p55 receptor which do not affect plasma lipoprotein concentrations or compositions.

Feeding of this particular atherogenic diet has been linked to the induction of inflammatory genes and the regulatory factor, NF-κB (41). Although the expression of TNF and its receptors were not studied directly, it is possible that TNF expression was also induced by the atherogenic diet, since NF-κB participates in the regulation of TNF gene expression (41, 42). However, the hypertriglyceridemia normally associated with systemic TNF release was not observed in our mice suggesting that either TNF expression is not provoked by the diet, or that TNF is induced and utilized within specific tissues. This is currently under study, as are the effects of particular dietary ingredients on the expression of TNF and its receptors. Regardless of any changes in expression of TNF due to feeding the atherogenic diet, it is clear that the activity of p55 cannot entirely protect against the combination of events leading to atherosclerosis in C57BL/6 mice, since the wild type animals did develop fatty streak lesions.

Since TNF affects the activities of endothelial cells, macrophages, and smooth muscle cells (3, 5, 12, 37, 38), loss of the p55 receptor could lead to changes in the cellularity or overall character of lesions. We found that lesions in p55-null mice were similar in overall character to those seen in cholesterol-fed wild type mice. Both strains showed fatty streak lesions in the proximal aortic sinus. The main cell type was macrophages, consistent with other reports of C57BL/6 lesions (28, 39). The macrophages in both strains were activated as evidenced by strong immunocytochemical staining for iNOS. Smooth muscle cells were absent from all lesions examined.

Despite these similarities, the lesions of p55-null mice contained less cell nuclei per lesion area as compared with wild type mice. This result suggests that differences exist between strains with respect to the proliferation, migration, and/or death of macrophages. Since many responses associated with the production of TNF are considered to promote artery wall

![Fig. 3. Comparison of the uptake and degradation of 125I-acetyl-LDL by peritoneal macrophages from wild type and p55-null mice.](http://www.jbc.org/)

![Fig. 4. Scavenger receptor immunohistochemical staining (red color) in aortic sinus lesions from wild type and p55-null mice.](http://www.jbc.org/)
macrophage accumulation (3–5, 8), eliminating p55 may have led to the reduced cell numbers. Overall lesion sizes were the same or larger for p55-null mice as compared with wild type mice suggesting that p55-null lesions accumulated a greater amount of cellular and/or extracellular lipid.

A probable mechanism by which p55 exerts limited protective function is by controlling scavenger receptor activity. Scavenger receptors are expressed by activated macrophages and are responsible for the uptake of modified lipoproteins. These pathways are thought to result in macrophage lipid accumulation and subsequent transformation of macrophages into foam cells at the artery wall (36). Using peritoneal macrophages to model events at the artery wall, we found that p55-null mice expressed 3-fold higher scavenger receptor activity than wild type mice based on the uptake and degradation of Ac-LDL. Consistent with this result, immunohistochemical studies showed increased type I and/or type II scavenger receptor protein expression in aortic sinus lesions of p55-null mice as compared with wild type mice.

Recent studies by Hsu et al. (43) showed TNF to down-regulate scavenger receptor gene expression and protein in macrophage cell line THP-1 via transcriptional and post-transcriptional processes. Down-regulation occurred even upon stimulation of scavenger receptor activity with M-CSF. Since elevations in M-CSF have been seen in C57BL/6 mice fed the atherogenic diet. This protection may be accomplished, in part, by down-regulation of scavenger receptor expression as well as the role of TNF receptor p55 in the atherogenic process. Further studies are aimed at determining the mechanism of p55 regulation of scavenger receptor expression as well as the role of TNF receptor p75 in the atherogenic process. By comparing the results we obtained from these studies with results observed in mice deficient in either TNF or lymphotixin, the role of each cytokine via its receptors in lesion development can be delineated.

Acknowledgments—We thank Dr. John F. Oram (Dept. of Medicine, University of Washington, Seattle, WA) for advice on the scavenger receptor assay and for helpful comments and suggestions when reviewing this manuscript. We thank Dr. Siamon Gordon (Sir William Dunn School of Pathology, Oxford, UK) for providing us with the 2FS antibody against mouse scavenger receptors. We thank Dr. Joseph Witzum (Dept. of Medicine, University of California, San Diego, CA) for providing us with antibodies against mouse scavenger receptor and for helpful discussions. We thank Dr. Jay Heinecke (Dept. of Medicine, Washington University, St. Louis, MO) for reviewing this manuscript, Randy Hall for assistance in maintaining the animal facility at Immunex Corporation, Inc., and Drs. Emil Chi and Ying-Tzang Tien (Dept. of Pathology, University of Washington) for their excellent technical support.

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J. Biol. Chem. 1996, 271:26174-26178.
doi: 10.1074/jbc.271.42.26174

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