Effects of IL-10 and age on IL-6, IL-1β, and TNF-α responses in mouse skeletal and cardiac muscle to an acute inflammatory insult

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MATERIALS AND METHODS

Experimental design. Young adult (4 mo old) and mature adult (10–11 mo old) male IL-10−/− (Jackson labs strain B6.129P2-Ili10tm1Cgn/J) or the background strain (C57BL/6J) IL-10+/+ control mice were assigned to one of the following groups (n = 12/group): young IL-10−/−, mature IL-10−/−, young IL-10+/+, and mature IL-10−/−. Within each group, animals were randomly divided into saline- and LPS-treated groups, resulting in eight groups (n = 6 per group). The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

The IMPORTANCE of understanding factors that regulate inflammatory cytokine expression, especially as an individual ages, is critical because elevated cytokine levels are implicated in many of the deleterious changes that occur in aging humans, such as reduced muscle strength and cardiovascular disease. Critical because elevated cytokine levels are implicated in proinflammatory cytokine expression, especially as an individual ages, is that IL-10, an anti-inflammatory cytokine, is an important regulator of IL-6, TNF-α, and IL-1β responses to inflammatory stimuli and that reduced levels of IL-10 contribute to elevated inflammatory responses often observed with aging. However, no studies to date have investigated how the anti-inflammatory cytokine IL-10 impacts expression of IL-6, TNF-α, and IL-1β in skeletal and cardiac muscle in response to an inflammatory insult in both young and mature mice. Thus our primary objective was to test the hypothesis that the absence of IL-10 is associated with greater IL-6, TNF-α, and IL-1β responses in skeletal and cardiac muscle and that aging further exaggerates these responses. Our primary objective was to test the hypothesis that the absence of IL-10 is associated with greater IL-6, TNF-α, and IL-1β responses to an inflammatory challenge in mouse skeletal and cardiac muscle and that aging further exaggerates these responses. We compared IL-6, IL-1β, and TNF-α mRNA and protein levels in skeletal and cardiac muscle of young (4 mo) and mature (10–11 mo) wild-type (IL-10+/+) and IL-10−/− mice following LPS. Skeletal and cardiac IL-6 mRNA and protein were elevated by LPS for IL-10+/+ and IL-10−/− mice with greater responses in the IL-10−/− mice (P<0.01). In skeletal muscle these effects were greater in mature than young mice (P<0.01). IL-1β mRNA and protein responses to LPS were greater in cardiac muscle of young but not mature IL-10−/− mice compared with IL-10+/+ (P<0.01). However, IL-1β responses were greater in mature than young mice, but only in IL-10−/− groups (P<0.05). The absence of IL-10 was associated with higher TNF-α protein levels in cardiac muscle (P<0.05). The results provide the first in vivo evidence that the absence of IL-10 is associated with a greater IL-6 response to LPS in skeletal and cardiac muscles, and in skeletal muscle aging further exaggerates these responses.

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Because IL-10−/− mice develop colitis after 11–12 mo, healthy mature adults (10–11 mo old) were used. All experiments were performed at the same time of day (late morning) for all groups, and mice had ad libitum access to water and rodent chow.

Sterile saline or LPS (serotype 0127:B8, Sigma) was injected intraperitoneally at a dose of 0.33 g/kg in 0.1 ml. Four hours postinjection, mice were euthanized by carbon dioxide inhalation, and both gastrocnemius muscles and the heart were quickly removed, trimmed of excess fat and connective tissue, wet weighed, frozen on dry ice, and stored at −80°C until subsequent analysis. For skeletal muscle analyses, one gastrocnemius was used for protein and the other for mRNA. The heart was cut along the sagittal plane with one half used for mRNA and the other for protein analyses. Pilot studies showed no regional differences in mRNA or protein expression in the heart. Experiments were approved by the Animal Use Committee at the University of Illinois and followed the American Physiological Society Animal Care Guidelines.

**mRNA analyses.** Muscle samples (50–60 mg) were homogenized in 1 ml of TRIReagent (Molecular Research Center, Cincinnati, OH), and RNA was extracted according to the manufacturer’s protocol. DNase (Stratagene, La Jolla, CA) treatment was performed according to manufacturer’s protocol. RNA concentration was determined with a spectrophotometer and stored at −80°C. Quantitative real-time RT-PCR was used to determine the expression of IL-6, TNF-α, and IL-1β mRNA relative to β-actin. Total RNA (1 μg) from each muscle sample was reverse-transcribed using the StrataScript first-strand synthesis system (Stratagene). A 1-μl aliquot of the reverse transcription product was added to a reaction mix containing 1× Full Velocity SYBR Green (Stratagene) and 150 nM of the IL-6, TNF-α, IL-1β, or β-actin primer pairs. RT-PCR were performed with a Stratagene MX3000P with the following parameters: a denaturing step at 95°C for 5 min, followed by 40 cycles of 1 s at 95°C and 30 s at 60°C. The primer sequences were as follows: β-actin, forward 5′-ctgtgctgca-cagcct-3′ and reverse 5′-ctcttgatcagcaccg-3′; IL-6, forward 5′-ctgggaagactgtgga-3′ and reverse 5′-tgcaagttcatcttggt-3′; TNF-α, forward 5′-accccttcgctgtca-3′ and reverse 5′-ctcttgagctgtcta-3′; and IL-1β, forward 5′-ggctatccatcttc-3′ and reverse 5′-cctctgcagacttg-3′ (Operon); and generated fragments of 209, 191, and 242 bp, respectively. Fluorescence measurements were taken at the end of each cycle (60°C product extension period). After amplification, a melting curve analysis was performed to verify amplification product specificity and absence of primer-dimer complexes. The efficiency of all primer pairs was determined and yielded similar efficiencies of 95–99% (r² > 0.98). In initial experiments, PCR products were separated on 2% agarose gels, stained with ethidium bromide, and photographed under UV light to validate that the PCR products were the appropriate size and no artifact bands were present. All PCR reactions were performed in duplicate for each reverse transcription product. Relative expressions of IL-6, TNF-α, and IL-1β were normalized by subtracting the corresponding β-actin threshold cycle (Ct) values and using the ΔΔCt comparative method (41). β-Actin Ct values were not different across genotype, treatment, and age. Data are expressed as fold changes relative to saline control in young IL-10−/− mice.

**Protein analyses.** Gastrocnemius and heart (50–60 mg) muscles were homogenized in 10 vol of an ice-cold buffer containing 50 mM Tri-HCl (pH 7.8), 2 mM potassium phosphate, 2 mM EDTA, 10% glycerol, 1% Triton X-100, 1 mM dithiothreitol, 3 mM benzamidine, 1 mM sodium orthovanadate, 10 mM leupeptin, 5 mg/ml aprotinin, and 1 mM 4-(2-aminoethyl) benzenesulfonyl fluoride) using a motor-driven glass pestle. The homogenate was immediately centrifuged at 12,000 g for 20 min at 4°C, and the supernatant was removed as the detergent-soluble fraction. Protein concentrations were determined using the Bio-Rad Protein Assay with BSA for the standard curve. Samples were stored immediately in aliquots at −80°C for subsequent ELISA analysis. IL-6, TNF-α, IL-1β, and IL-10 concentrations were measured in skeletal and cardiac muscle lysates by validated kits (Endogen, IL) with a detection limit of 7, 9, 3, and 12 pg/ml, respectively. The kits were further validated with our tissue supernates by serial dilution curves and negative controls. Cytokine values were normalized for protein content and are expressed as picograms per milligram protein.

**Statistical analyses.** All data are presented as means ± 1 SE. Data for all cytokines at the protein and mRNA levels across treatments passed the normality test (alpha P = 0.05), and the statistical model was a three-way factorial ANOVA (age × treatment × genotype). Univariate three-way ANOVA was used to assess main effects of genotype (IL-10−/− vs. IL-10+/–), treatment (saline vs. LPS), and age (young vs. mature), as well as interactions between genotype, treatment, and age for all variables. If significant main effects or interactions were found, group differences were analyzed by independent t-test, corrected for familywise type I error by modified Bonferroni. A two-way ANOVA was performed on the IL-10 protein data to assess the main effects of treatment and age. If significant differences were found, the Bonferroni post hoc test was used to determine the source of the difference. Pearson correlation coefficients were calculated between cytokines at the protein level both within and between skeletal and cardiac muscle, with significant values flagged at P < 0.05 (2-tailed). All analyses were performed with SPSS 15.0 with the significance level set at P < 0.05.

**RESULTS**

**Body weights.** Initial body weights were not different among groups (25.3 ± 0.6, 30.5 ± 2.0, 25.6 ± 1.0, and 28.5 ± 1.2 g for young and mature IL-10−/− and young and mature IL-10−/− mice, respectively). Additionally, no significant changes in body mass occurred within 4 h of LPS or saline exposure.

**IL-6 mRNA and protein expression.** There were significant main effects of genotype, age, and treatment on IL-6 mRNA and protein levels in skeletal muscle, with significant interactions between age and genotype, age and treatment, genotype and treatment, and age, genotype, and treatment (Fig. 1, A and B). In skeletal muscle, LPS was associated with significant increases in IL-6 mRNA in all groups relative to the corresponding saline controls and a significantly greater IL-6 mRNA response in all mature groups compared with the respective young groups (Fig. 1A). With respect to genotype, LPS was associated with 4.0- and 5.5-fold greater increases in IL-6 mRNA in young and mature IL-10−/− mouse skeletal muscle than the corresponding IL-10+/– groups, respectively. At the protein level, LPS was associated with significant increases in IL-6 mRNA in all groups relative to the corresponding saline controls and a significantly greater IL-6 mRNA response in all mature groups compared with the respective young groups (Fig. 1A). With respect to genotype, LPS was associated with 4.0- and 5.5-fold greater increases in IL-6 mRNA in young and mature IL-10−/− mouse skeletal muscle than the corresponding IL-10+/– groups, respectively. At the protein level, LPS was associated with significant increases in skeletal muscle IL-6 compared with saline controls in all groups, and these responses were significantly greater in both mature groups compared with their respective young groups (Fig. 1B). With respect to genotype, LPS was associated with 3.9- and 4.1-fold greater IL-6 protein levels in IL-10−/– young and mature mice than the corresponding IL-10+/– groups, respectively.

In cardiac muscle, there were significant main effects of genotype and treatment on IL-6 mRNA levels, with a significant interaction between genotype and treatment (Fig. 1C). LPS was associated with a significant increase in IL-6 mRNA in cardiac muscle in all groups relative to the corresponding saline controls (Fig. 1C). Additionally, with respect to genotype, LPS was associated with 18- and 6.9-fold greater IL-6 mRNA responses in cardiac muscle of young and mature IL-10−/– mice than the corresponding IL-10+/– mice, respectively. At the protein level, LPS was associated with significant 2.5- and 3.1-fold increases in IL-6 over saline levels in respec-
tive young and mature cardiac muscle only in the IL-10−/− groups (Fig. 1D). IL-6 protein responses across ages and genotypes were highly correlated in cardiac and skeletal muscle ($r = 0.845$).

**IL-1β mRNA and protein expression.** In skeletal muscle, there were significant main effects of age and treatment on IL-1β mRNA levels, with a significant interaction between age and treatment (Fig. 2A). LPS was associated with a significantly greater IL-1β mRNA response in skeletal muscle relative to the respective saline groups (Fig. 2A). With respect to genotype, the IL-1β mRNA response in skeletal muscle was reduced in the younger but not the mature-IL-10−/− group relative to the corresponding IL-10−/+ group (9.5- vs. 15.5-fold increases for young IL-10−/+ and IL-10−/+ mice, respectively). None of the experimental variables were found to have a significant effect on IL-1β protein levels in skeletal muscle (Fig. 2B).

In cardiac muscle, there were significant main effects for treatment on IL-1β mRNA levels, with significant interaction effects between genotype and age and genotype and age and...
treatment (Fig. 2C). There were significant increases in IL-1β mRNA in response to LPS in all groups relative to the corresponding saline control. However, in contrast to skeletal muscle, the IL-1β mRNA response was significantly greater in the young but not mature IL-10−/− mice than the corresponding IL-10+/+ groups (37.5- vs. 15.5-fold increases for young IL-10−/− and IL-10+/+, respectively). There were significant main effects of genotype and treatment on IL-1β protein levels in cardiac muscle (Fig. 2D). In IL-10+/+ mice, IL-1β levels after LPS were significantly greater in mature than young adult mice. The effects of genotype were evidenced in young but not mature mice by significantly higher IL-1β levels after LPS in IL-10−/− than IL-10+/+ mice.

**TNF-α mRNA and protein expression.** No significant main effects or interactions were found for age, genotype, or treatment on TNF-α mRNA expression in either skeletal or cardiac muscle (Fig. 3, A and B). None of the experimental variables were found to have a significant effect on TNF-α protein levels in skeletal muscle, while in cardiac muscle, genotype was found to have a significant main effect on TNF-α protein levels (Fig. 3, C and D).

**IL-10 protein expression.** In skeletal muscle, there was a significant main effect of treatment on IL-10 protein levels (Table 1). In the young IL-10+/+ mice there was a significant 3.0-fold increase in skeletal muscle IL-10 in response to LPS relative to saline. In cardiac muscle, there were significant main effects of both treatment and age on IL-10 protein levels.

## DISCUSSION

The present findings provide novel in vivo evidence that the absence of IL-10 dramatically increases the IL-6 response to an acute inflammatory insult in both skeletal and cardiac muscle. Furthermore, these effects in skeletal muscle are significantly impacted by age. Physiologically, the significance of these findings is highlighted by the fact that skeletal muscle comprises the largest organ system in the body (40–50% of body mass) and thus can play a pivotal role in responses to an inflammatory insult. For example, IL-6 was the first cytokine to be named a “myokine” due to the significant amount of this cytokine produced by muscle tissues (10, 24, 33, 44) and its potential roles in inflammation and metabolism in humans (31, 32, 34). In skeletal muscle, mature adult mice demonstrated higher IL-6 mRNA and protein levels in response to LPS than the corresponding treatment- and genotype-matched saline groups. In cardiac muscle, the absence of IL-10 was associated with significantly greater expression of IL-6 mRNA and protein in response to LPS; however, these differences were unaffected by age.

The dramatic rise in IL-6 mRNA observed in both skeletal and cardiac muscle within 4 h of LPS injection indicate that increases in gene transcription contributed to the increased levels of IL-6 protein. Previous literature indicates that these

### Table 1. IL-10 protein concentrations in skeletal and cardiac muscle for IL-10+/+ mice 4 h following intraperitoneal saline or LPS

<table>
<thead>
<tr>
<th></th>
<th>Young</th>
<th>Mature</th>
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<tbody>
<tr>
<td><strong>Skeletal IL-10, pg/mg</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline</td>
<td>37±5</td>
<td>42±13</td>
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<tr>
<td>LPS</td>
<td>113±12*</td>
<td>84±15</td>
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<tr>
<td><strong>Cardiac IL-10, pg/mg</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline</td>
<td>207±51</td>
<td>108±22</td>
</tr>
<tr>
<td>LPS</td>
<td>307±53</td>
<td>207±40</td>
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Values are means ± SE; n = 6/group. *P < 0.05 compared with saline within age. There was a significant main effect of age and treatment for cardiac IL-10 at P < 0.05.

![Fig. 3. LPS-induced changes in TNF-α mRNA and protein in skeletal (A and B) and cardiac (C and D) muscle of young or mature adult IL-10−/− and IL-10+/+ mice 4 h following ip saline or LPS. mRNA data are expressed as fold changes relative to saline control in young IL-10−/− mice. There were no significant main effects or interaction effects for TNF-α mRNA expression in skeletal or cardiac muscle. There was a significant main effect of genotype on TNF-α in cardiac muscle. There are presented as means ± SE with significance set at P < 0.05.](image-url)
increases in skeletal muscle cytokine expression are mediated through toll-like receptor 4 (TLR-4), as the response to LPS exposure is absent in mice lacking functional TLR-4 (17, 18). Further, in skeletal muscle, IL-6 can act in an autocrine manner to increase its own production via both transcriptional and translational mechanisms (24, 51). Cardiomyocytes also express TLR-4 (14) and a functional TLR-4 is necessary for LPS-induced cytokine expression (4) and myocardial depression (5). While our present in vivo experiments do not directly determine the cell types contributing to the increased cytokine production, previous reports have clearly shown that skeletal (16, 17, 23, 28, 44) and cardiac (28, 37, 50) muscle produce numerous cytokines, including TNF-α, IL-1β, and IL-6 in response to LPS. However, microvascular cells have also been shown to significantly contribute to the IL-6 response to LPS in cardiac muscle (37). Regardless of the cell type synthesizing these cytokines, these data show that the inflammatory environment in both skeletal and cardiac muscle can be strongly impacted by both genotype and age.

The increases in IL-6 mRNA observed in response to LPS in IL-10+/+ mice in the present study are supported by reports in rat skeletal and cardiac muscle (28), mouse skeletal muscle (16), and human skeletal muscle (26). The increases in IL-6 in cardiac muscle in response to an inflammatory insult are in agreement with earlier work demonstrating marked increases in IL-6 mRNA within 3–6 h of LPS (28, 37, 39, 50). The novelty of the present findings is that in both cardiac and skeletal muscle, the IL-6 mRNA responses to LPS were significantly greater in IL-10−/− than IL-10+/+ mice. However, only in skeletal muscle was age associated with a significantly greater IL-6 mRNA response. The finding that the cardiac IL-6 mRNA response to LPS was not significantly greater in mature than younger adult mice is supported by the report that LPS-induced IL-6 mRNA expression is only gradually increased with age (37). Specifically, increases in IL-6 mRNA were not significantly different between 4- and 10-mo-old CB6 mice; however, responses in 16- to 17-mo-old or 23- to 27-mo-old mice were significantly greater than either of the younger groups (37).

Similar to the mRNA changes, IL-6 protein levels were dramatically higher in the absence of IL-10, which agrees with previous work showing that in other organs (liver, spleen, brain) IL-10 deficiency increases the IL-6 response to LPS (1, 55). The higher IL-6 protein levels in cardiac compared with skeletal muscle are supported by previous work showing that LPS-induced increases in IL-6 mRNA are greater in cardiac muscle compared with other tissues, including skeletal muscle (38). Importantly, higher levels of IL-6, which has both profound anti-inflammatory properties (46), can have dramatic effects on the function and integrity of both skeletal and cardiac muscles. IL-6 has been implicated in skeletal muscle atrophy (19, 22, 48), and elevated plasma IL-6 in humans is associated with increased loss of muscle mass and strength (3, 40, 49). In cardiac muscle, high levels of IL-6 have been shown to suppress cardiac function (11, 12) and are associated with heart failure in humans (7). In contrast, increases in plasma IL-6 have been shown to increase expression of anti-inflammatory cytokines, including IL-10 and IL-1 receptor antagonist (IL-1ra) in humans (43). Further, infusion of recombinant IL-6 has also been shown to reduce the systemic TNF-α response to LPS in both humans (42) and mice (29). In IL-6-deficient mice treated with LPS, higher levels of IL-1β and TNF-α in cardiac muscle (38) and higher levels of TNF-α in plasma (52) have been observed, suggesting that IL-6 may help to downregulate these cytokines. However, IL-6 inhibition of TNF-α may be organ specific, as evidenced by the report that when IL-6-deficient mice were injected intracerebroventricularly with LPS, no differences in TNF-α production were observed in the brain, while in the liver and spleen TNF-α levels were increased up to fourfold (8).

The finding that age significantly impacted IL-6 in skeletal but not cardiac muscle highlights the interesting finding that the regulation of IL-6 may be more sensitive to age-related changes in skeletal muscle compared with cardiac muscle. Moreover, this increased sensitivity with aging may be due in part to reduced levels of IL-10 as evidenced by the significantly greater response in mice lacking IL-10 than wild-type controls. This is further supported by a blunted IL-10 response to LPS in skeletal muscle in mature relative to young IL-10+/+ mice. Taken together, this highlights the potential importance of IL-10 in maintaining normal levels of IL-6 in skeletal muscle. Clinically, this may be significant based on the aforementioned effects of IL-6 on skeletal muscle function and integrity. While short-term increases in IL-6, such as during exercise (34) or acute inflammation, may not have deleterious effects on muscle function, it has been suggested that prolonged elevations in IL-6 can be harmful (39). For example, infusion of modest levels of IL-6 (0.7 pg·muscle−1·h−1) for 14 days into the muscles of otherwise healthy animals was associated with significant muscle atrophy (22). Significant muscle atrophy has been reported in the gastrocnemius of transgenic mice overexpressing IL-6 (47), and this atrophy was blocked by treatment with an IL-6 receptor antibody (48). Functional muscle deficits are associated with chronically elevated plasma IL-6 as evidenced by its inverse correlation to quadriceps strength (54) and grip strength, an indicator of whole body strength, in the elderly (3, 49).

The majority of age- and/or IL-10-mediated effects on IL-1β were observed in cardiac muscle. In young IL-10−/− mice, both IL-1β mRNA and protein responses to LPS in cardiac muscle were greater than the corresponding IL-10+/+ mice. With respect to age, the significantly greater IL-1β mRNA and protein response to LPS in mature than young mouse cardiac muscle expands previous knowledge showing that the IL-1β response to LPS tended to increase in aged mouse cardiac muscle (37). The present results reinforce that aging may exaggerate cardiac IL-1β responses at both the mRNA and protein levels. These changes likely have functional significance since IL-1β is implicated in reduced human myocardial function during sepsis (27). Thus, while LPS-induced increases in IL-6 showed the most sensitivity to age-associated changes in skeletal muscle, IL-1β showed the most sensitivity to age-related changes in cardiac muscle. Several possibilities may explain why the IL-1β responses were not as dramatic as the IL-6 responses. First, IL-1β, like TNF-α, peaks earlier than IL-6, and thus our analysis did not capture the peak IL-1β response (2). Second, subsequent increases in IL-1ra may have prevented even greater increases in IL-1β responses since high levels of IL-6 have been shown to increase plasma IL-1ra in humans (43). However, the IL-1β responses in cardiac muscle were not further increased by the absence of IL-10, suggesting
at least in mature mice, the exaggerated IL-1β responses are likely not due to reduced anti-inflammatory actions of IL-10.

While a significant TNF-α response to LPS was not found in the present experiments, there was a significant effect of genotype on TNF-α protein levels in cardiac muscle. In both young and mature adult mice, TNF-α protein levels were higher in IL-10+/− than IL-10−/− mice, supporting previous evidence demonstrating that IL-10 can inhibit TNF-α at the translational level in inflammatory cells (9, 25). Thus, regardless of age, IL-10 is associated with reduced TNF-α protein levels in cardiac muscles under basal or inflammatory states as has been shown in other tissues (1, 55). Functionally, this could be significant as a synergistic depression of human myocardial function by TNF-α and IL-1β has been reported (27).

The absence of a significant TNF-α response to LPS in the present study may be due to the magnitude and kinetics of TNF-α responses to LPS compared with IL-6. For example, fold increases in TNF-α mRNA in skeletal muscle were 7- to 10-fold lower than IL-6 increases 2 h post-LPS (17, 28). However, there is evidence that LPS-induced increases in TNF-α mRNA would not be significantly impacted by age as no difference in the responses between 4- and 24-mo-old mice were found 1 h after LPS injection (37).

These experiments utilizing in vivo genetic model have provided novel data demonstrating that both age and IL-10 are strong physiological regulators of the IL-6 response to LPS in skeletal muscle. Interestingly, we found that IL-10, but not age, significantly impacted the cardiac IL-6 response. In the present experimental model, it is not surprising that the most striking effects were observed for IL-6 since skeletal muscle produces significant amounts of IL-6 (16, 17, 23, 28, 44), and LPS-induced increases in IL-6 in cardiac muscle have been shown to be greater than other cytokines, including TNF-α and IL-1β (37).

Importantly, while IL-6 has both pro- and anti-inflammatory actions, the existing literature suggest that chronic elevations in IL-6 are associated with deleterious changes in skeletal and cardiac muscle. In skeletal muscle, these results clearly demonstrate the importance of anti-inflammatory cytokines, such as IL-10, in reducing the exaggerated IL-6 responses that are observed with aging.

GRANTS

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