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Interleukin-33/ST2 system attenuates aldosterone-induced adipogenesis and inflammation

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ABSTRACT

Interleukin-33 (IL-33) but not soluble ST2 (sST2) exerts anti-inflammatory and protective effects in several tissues. Aldosterone, a proinflammatory mediator which promotes adipogenesis, is elevated in obese patients. The aim of this study was to investigate the interactions between IL-33/ST2 system and Aldosterone in adipose tissue. Rats fed a high fat diet presented increased sST2 expression, diminished IL-33/sST2 ratio and enhanced levels of differentiation and inflammation in adipose tissue as compared to controls. A similar pattern was observed in adipose tissue from C57BL/6 Aldosterone-treated mice. In both animal models, Aldosterone was correlated with sST2. Treatment of 3T3-L1 adipocytes with IL-33 delayed adipocyte differentiation diminished lipid accumulation and decreased inflammation. Aldosterone decreased IL-33 and increased sST2 expressions in differentiated adipocytes. Aldosterone-induced adipocyte differentiation and inflammation were blocked by IL-33 treatment, but sST2 did not exert any effects. The crosstalk between IL-33/ST2 and Aldosterone could be relevant in the metabolic consequences of obesity.

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1. Introduction

Interleukin (IL)-33 (also known as IL-1F11) was identified as a new member of the IL-1 cytokine family (Schmitz et al., 2005) with dual function, acting both as a traditional cytokine and as an intracellular nuclear factor with transcriptional regulatory properties (Li et al., 2000) through binding to the receptor ST2. ST2 gene encodes at least 3 isoforms of ST2 proteins by alternative splicing: ST2L, a transmembrane isoform; sST2, a secreted soluble ST2 form that lacks the transmembrane and intracellular domains; and ST2V, a variant form mainly present in the gut of humans (Tago et al., 2001). The expression of the components of the IL-33/ST2 system has been reported in many tissues, including myocardium (Bartunek et al., 2008), coronary artery endothelium (Demyanets et al., 2013) and aorta (Martinez-Martinez et al., 2013), where it plays a role in cardiac and vascular remodelling as well as in inflammation.

Obesity is a proinflammatory condition in which hypertrophied adipocytes contribute to increase circulating levels of proinflammatory cytokines. The obesity-associated state of chronic low-grade systemic inflammation, termed "metabolic inflammation," is a key factor in the pathogenesis of insulin resistance and type 2 diabetes (Makki et al., 2013). Obesity is the result of increase in the adipocyte number size. Mature adipocytes arise from differentiation of preadipocytes and progenitor cells which reside in adipose tissue. Therefore, controlling this process could modulate the consequences of adipose tissue remodeling that occurs in obesity. Recent data described that the IL-33/ST2 system plays an important role in adipose tissue (Miller et al., 2010; Zeyda et al., 2013) and in vascular alterations associated with obesity (Martinez-Martinez et al., 2013). Thus, IL-33 administration has been shown to decrease fat mass and to reduce the chronic inflammatory response associated with obesity in mice (Miller et al., 2010). Moreover, circulating sST2 is increased in severely obese patients (Zeyda et al., 2013) and its levels correlate with classic and novel markers of insulin resistance and endothelial dysfunction (Miller

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et al., 2012). However, the precise and integrative role of IL-33/ST-2 pathway components in the pathogenesis of adipocyte differentiation associated with obesity is still unknown.

Aldosterone (Aldo) can be produced by adipose tissue (Briones et al., 2012) and its levels are higher in overweight/obese individuals, particularly those with excess visceral fat (Rossi et al., 2008) and in diabetic patients (Underwood and Adler, 2013). It is also now considered to be a risk factor for metabolic and cardiovascular diseases (Engeli et al., 2003; Krug and Ehrhart-Bornstein, 2008). In 3T3-L1 pre-adipocytes, Aldo increased mRNA levels of pro-inflammatory adipokines (Guo et al., 2008; Hoppmann et al., 2010) and promotes adipogenesis (Briones et al., 2012; Caprio et al., 2007; Rondinone et al., 1993). In fact, chronic exposure to Aldo of 3T3-L1 cells induced remarkable changes in morphological, biochemical and molecular markers of differentiation, through specific activation of mineralocorticoid receptor (MR) (Rondinone et al., 1993). Importantly, MR antagonism is able to block adipocyte differentiation in human primary preadipocytes from different fat depots, giving to the MR a clearly relevant role in the pathophysiology of adipose tissue dysfunction (Caprio et al., 2011). However, some of the mechanisms and possible interaction with other systems remain unknown.

The aims of this study were to evaluate the expression and the effects of the IL-33/ST2 system in adipogenesis and whether these effects could be modulated in a situation of adipose tissue remodeling such as obesity. In addition, we have explored if the effects of Aldo in adipose tissue could be modulated by the IL-33/ST2 system.

2. Materials and methods

2.1. Animals

The investigation was performed in accordance with the Guide for Care and Use of Laboratory Animals published by the U.S. National Institutes of Health (publication no. 82-23, revised in 1996) and were approved by the Animal Care and Use Committee of Universidad Complutense de Madrid and by the local ethical committee "Comité regional Nancy-Lorraine/Nord-Est" (no. B54-547-20). Studies were performed in 150 g male Wistar rats (Harlan Ibérica, Barcelona, Spain). Rats were housed at constant room temperature (20–22 °C), humidity (50–60%), with light cycle (12:12 light–dark) with free access to a standard diet (3.5% fat; Harlan Teklad #TD.2014, MN, USA, n = 7) or a high fat diet (HFD, 33.5% fat; Harlan Teklad #TD.03307, MN, USA, n = 7) for 6 weeks. Body weight was measured once a week. Blood pressure (SBP) was estimated basally and at the end of the study by use of a tail-cuff plethysmograph (Narco Bio-Systems, Houston, Texas, USA) in unrestrained animals as previously reported (Maeso et al., 1998).

Adult male C57BL/6 wild-type mice (JANVIER LABS, Saint Berthevin, France) were infused for 3 weeks with Aldo (1 mg/kg/day) or vehicle (150 mmol/l NaCl, 5% ethanol) using an osmotic minipump (Alzet, Cupertino, CA, USA) (n = 7, each group). Tail cuff blood pressure was monitored throughout the treatment.

For euthanasia, animals were anesthetized i.p. with a cocktail of ketamine 70 mg/kg (Imalgene 1000, Merial, France) and xilacine 6 mg/kg (Rompun 2%, Leverkusen, Germany). Serum and plasma were collected and abdominal adipose tissue was dissected for analysis.

2.2. Histological evaluation

Adipose tissue from rats and mice was quickly cleaned from the surrounding tissues and blood, fixed in formalin 37% and embedded in paraffin blocks. Afterwards, 5 μm thick sections were cut with a rotational microtome (Leitz 1512, IMEB INC, Chicago, IL, USA), placed onto glass microscope slides and stained with hematoxylin and eosin by routine methods. Adipocyte size was quantified by planimetry using an image analyzer (LAS, LEICA). All measurements were performed blind and calibrated with known standards.

2.3. Immunohistological evaluation

Paraffin-embedded adipose tissue sections (5 μm) were used. Slides were treated with H_2O_2 for 10 min to block peroxidase activity. All samples were blocked with 5% normal goat serum in PBS for 1 h and incubated for 1 h with anti-IL-33 (Santa Cruz Biotechnology, Santa Cruz, CA, USA; dilution 1:25), ST2 (Novus Biologicals, Cambridge, UK; dilution 1:50), IRAK-1 (Santa Cruz Biotechnology, dilution 1:25), MyD88 antibodies (Santa Cruz Biotechnology, Santa Cruz, CA, USA; dilution 1:25), washed three times, and then incubated for 30 min with the horseradish peroxidase-labeled polymer conjugated to secondary antibodies (Dako Cytomation, Glostrup, Denmark). The signal was revealed by using DAB Substrate Kit (BD Pharmingen, San Diego, CA, USA). As negative controls, samples followed the same procedure described earlier but in the absence of primary antibodies.

2.4. 3T3-L1 cells

Murine 3T3-L1 preadipocytes (Cambridge Bioscience, Cambridge, UK) were grown until confluence in DMEM (Invitrogen, Grand Isaland, NY, USA) containing 4.5 g/l D-glucose (Sigma, St Louise, MO, USA), 10% FCS (Sigma, St. Louis, MO, USA), 100 U/ml penicillin and 100 μg/ml streptomycin (Sigma, St. Louis, MO, USA). 3T3-L1 adipocyte differentiation was initiated by the addition of a cocktail containing 100 μmol/l 3-isobutyl-1-methylxanthine, 175 nmol/l insulin and 250 nmol/l dexamethasone for 48 hours (day 0). Cells were then maintained in DMEM with 10% FCS and 175 nmol/l insulin in the presence or absence of IL-33 (0.01 μg/ml, R&D Systems, MN, USA), sST2 (2 μg/ml, R&D Systems, MN, USA), Aldo (10^{-8} M, Sigma, St. Louis, MO, USA), eplerenone (10^{-6} M, Sigma, St. Louis, MO, USA) or combination of these stimuli for 2, 4 and 6 days. In another set of experiments, cells were cultured in steroid-depleted medium supplemented with 10% dextran-coated charcoal-treated serum (Hyclone, Logan, UT, USA). The doses of IL-33 and sST2 were chosen based on previous studies (Martinez-Martinez et al., 2013).

For morphological determination of cell lipid content, cells were fixed in 5% formaldehyde in PBS, washed, then stained with oil red O (Sigma, St. Louis, MO, USA).

2.5. Real time reverse-transcription PCR

Abdominal adipose tissue was immediately frozen in liquid nitrogen for molecular studies. Total RNA was extracted with Trizol Reagent (Euromedex, Souffelweyersheim, France) and purified using the RNeasy kit, according to the manufacturer's instructions (Qiagen, Hilden, Germany). Reverse-transcription was performed using RevertAid Reverse Transcriptase (Fermentas, France). First strand cDNA was synthesized according to the manufacturer's instructions (Roche, Mannheim, Germany). Quantitative PCR analysis was then performed with SYBR green PCR technology (ABGene, Surrey, UK) (Tables S1 and S2). Relative quantification was achieved with MyiQ (Bio-Rad, Hercules, CA, USA) software according to the manufacturer's instructions. Data were normalized by GADPH levels and expressed as percentage relative to controls. All PCRs were performed at least in triplicate for each experimental condition.

2.6. ELISA

IL-33, and sST2 concentrations in supernatants and ST2L in cell extracts from cells, and adipose tissue homogenates from mice were

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