Diabetologia (2011) 54:2660–2668
DOI 10.1007/s00125-011-2248-8

ARTICLE

Critical role of chemokine (C-C motif) receptor 2 (CCR2) in the KK*Ay*$^{+}$*Apoe*$^{-/-}$ mouse model of the metabolic syndrome

H. G. Martinez · M. P. Quinones · F. Jimenez · C. A. Estrada · K. Clark · G. Muscogiuri · G. Sorice · N. Musi · R. L. Reddick · S. S. Ahuja

Received: 31 May 2011 / Accepted: 3 June 2011 / Published online: 21 July 2011

Abstract
Aims/hypothesis Chemokines and their receptors such as chemokine (C-C motif) receptor 2 (CCR2) may contribute to the pathogenesis of the metabolic syndrome via their effects on inflammatory monocytes. Increased accumulation of CCR2-driven inflammatory monocytes in epididymal fat pads is thought to favour the development of insulin resistance. Ultimately, the resulting hyperglycaemia and dyslipidaemia contribute to development of the metabolic syndrome complications such as cardiovascular disease and diabetic nephropathy. Our goal was to elucidate the role of CCR2 and inflammatory monocytes in a mouse model that resembles the human metabolic syndrome.
Methods We generated a model of the metabolic syndrome by backcrossing KK*Ay*$^{+}$ with *Apoe*$^{-/-}$ mice (KK*Ay*$^{+}$*Apoe*$^{-/-}$) and studied the role of CCR2 in this model system.
Results KK*Ay*$^{+}$*Apoe*$^{-/-}$ mice were characterised by the presence of obesity, insulin resistance, dyslipidaemia and increased systemic inflammation. This model also manifested two complications of the metabolic syndrome: atherosclerosis and diabetic nephropathy. Inactivation of *Ccr2* in KK*Ay*$^{+}$*Apoe*$^{-/-}$ mice protected against the metabolic syndrome, as well as atherosclerosis and diabetic nephropathy. This protective phenotype was associated with a reduced number of inflammatory monocytes in the liver and muscle, but not in the epididymal fat pads; circulating levels of adipokines such as leptin, resistin and adiponectin were also not reduced. Interestingly, the proportion of inflammatory monocytes in the liver, pancreas and muscle, but not in the epididymal fat pads, correlated significantly with peripheral glucose levels.
Conclusions/interpretation CCR2-driven inflammatory monocyte accumulation in the liver and muscle may be a critical pathogenic factor in the development of the metabolic syndrome.

Keywords Animal-mouse · Basic science · Cardiac complications · Experimental immunology · KO mice · Metabolic syndrome · Nephropathy

Abbreviations

CCL2	Chemokine (C-C motif) ligand 2
CCR2	Chemokine (C-C motif) receptor 2
GSK-3β	Glycogen synthase kinase 3β
GTT	Glucose tolerance test
HFD	High-fat diet

H. G. Martinez and M. P. Quinones contributed equally to this study.

Electronic supplementary material The online version of this article (doi:10.1007/s00125-011-2248-8) contains peer-reviewed but unedited supplementary material, which is available to authorised users.

H. G. Martinez · F. Jimenez · S. S. Ahuja
South Texas Veterans Health Care System,
Audie L. Murphy Division,
San Antonio, TX, USA

H. G. Martinez · F. Jimenez · C. A. Estrada · K. Clark · G. Muscogiuri · G. Sorice · N. Musi · S. S. Ahuja (✉)
Department of Medicine (MC 7870),
University of Texas Health Science Center at San Antonio,
7703 Floyd Curl Drive,
San Antonio, TX 78229-3900, USA
e-mail: ahuja@uthscsa.edu

M. P. Quinones
Department of Psychiatry, University of Texas Health Science Center at San Antonio (UTHSCSA),
San Antonio, TX, USA

R. L. Reddick
Department of Pathology, University of Texas Health Science Center at San Antonio (UTHSCSA),
San Antonio, TX, USA