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Role of perivascular adipose tissue in obesity-related vascular damage

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Most blood vessels are surrounded by adipose tissue. Similarly to the adventitia, perivascular adipose tissue (PVAT) was considered only as a passive structural support for the vasculature and it was routinely removed for isolated blood vessel studies. In 1991 Soltis and Cassis demonstrated for the first time that PVAT reduced contractions to noradrenaline in rat aorta. Since then, an important number of adipocyte-derived factors with paracrine vasoactive effects have been identified. Under physiological conditions PVAT releases a number of adipokines that elicit a beneficial effect on vascular function and are essential for the maintenance of vascular resistance. Moderate increases of PVAT in overweight situations lead to an adaptative overproduction of vasodilator factors in PVAT, probably aimed at protecting vascular function. Consequently, in situations of normal weight and moderate overweight the protective and beneficial role of perivascular adipokines increases in parallel to the amount of PVAT. In obesity, however, PVAT undergoes structural and functional changes losing its anticontractile properties by an increase of contractile, oxidative, and inflammatory factors, thus leading to endothelial dysfuntion. This unbalance towards a predominance of vasoconstrictor and inflammatory factors in obesity could provide the link between obesity, cardiovascular functional and

structural alterations and cardiovascular diseases. PVAT has been regarded until now as a homogeneous adipose tissue depot which is different from subcutaneous and other visceral adipose tissues. However, a large body of evidence now suggests regional phenotypic differences among PVAT depending on the specific vascular bed or even within different regions of a same blood vessel. PVAT heterogeneity seems to determine its physiological and pathophysiological relevance to vascular function and structure. The adipose-vascular axis may represent therefore novel targets for pharmacological intervention of vasculopathy in cardio-metabolic disorder. (Funded by BFU2011-25303, GR921645-Santander, Fundación Eugenio Rodriguez Pascual, Fundación Mutua Madrileña, and SESCAMET).

Short Biography

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My research has been devoted to the study of pathophysiological mechanisms in hypertension and obesity and the search for effective drugs to prevent and/or reverse cardiovascular damage. In recent years, my research has focused on the study of the relationship between excess weight (overweight and obesity) and the development of various cardiovascular diseases, as well as in characterizing some of the molecular mechanisms involved in their development. I have a particular interest in the study of the influence of perivascular adipose tissue, as a source of paracrine factors, on vascular function and structure. A better understanding of these mechanisms will allow evaluating new drugs and designing intervention strategies to prevent and/or slow the progression of cardiovascular disease associated with overweight and obesity.

Education

1981 – 1986 Study of Pharmacology at the Universidad Complutense of Madrid (Spain)

Scientific experience

1986 – 1990	Ph.D. Thesis at the Pharmacology Department of the Universidad Autónoma of Madrid (Spain) under supervision of Prof. Jesús Marín López
1990 – 1994	Marie Curie Postdoctoral Fellow at the Pharmacology Institute of the University of Heidelberg (Germany) with Prof. Detlev Ganten
1994 – 2003	Group Leader at the Pharmacology Institute of the Universidad Complutense de Madrid
7 – 10/2001	Research Fellow at the Cardiovascular Institute, University San Francisco California with Dr. Brian Black
Since 2003	Group leader at the Pluridisciplinar Institute of the Universidad Complutense de Madrid
2017 (Feb to May)	Fulbright Scholar at the Department of Physiology and Functional Genomics, University of Florida, Gainesville with Prof. Colin Sumners

Teaching experience

1990-1994	Visiting Assistant Professor in the Pharmacology Institute of the University of Heidelberg (Germany)
1994-2002	Lecturer at the Pharmacology Department of the Universidad Complutense of Madrid (Spain)
2002-2015	Senior lecturer at the Pharmacology Department of the Universidad Complutense of Madrid (Spain)
Since 2015	Professor at the Pharmacology Department of the Universidad Complutense of Madrid (Spain)

Selected publications

1. Role of Perivascular Adipose Tissue in Health and Disease. Maria S. Fernández-Alfonso, Beatriz Somoza, Dmitry Tsvetkov, Artur Kuczmanski, Mick Dashwood, Marta Gil-Ortega. Comp Physiol 8: 23-59, 2018.

2. Mild and Short-Term Caloric Restriction Prevents Obesity-Induced Cardiomyopathy in Young Zucker Rats without Changing in Metabolites and Fatty Acids Cardiac Profile. Ruiz-Hurtado G, García-Prieto CF, Pulido-Olmo H, Velasco-Martín JP, Villa-Valverde P, Fernández-Valle ME, Boscá L, Fernández-Velasco M, Regadera J, Somoza B, Fernández-Alfonso MS. Front Physiol. 8:42, 2017.

3. Role of PVAT in coronary atherosclerosis and vein graft patency: friend or foe? Fernández-Alfonso MS, Gil-Ortega M, Aranguez I, Souza D, Dreifaldt M, Somoza B, Dashwood MR. Br J Pharmacol 174:3561-3572, 2017

4. Caloric Restriction as a Strategy to Improve Vascular Dysfunction in Metabolic Disorders. García-Prieto CF, Fernández-Alfonso MS. Nutrients. 8(6), 2016. pii: E370.

5. Global cardiovascular protection in chronic kidney disease: caveats and potential improvers. Gema Ruiz-Hurtado, Pantelis Sarafidis, Maria Fernández-Alfonso, Bernard Waeber, and Luis Miguel Ruilope. Nature Reviews y Cardiology 13(10):603-8, 2016.

6. Role of matrix metalloproteinase (MMP)-9 in chronic kidney disease: a new biomarker of resistant albuminuria. Pulido-Olmo H, García-Prieto CF, Álvarez-Llamas G, Barderas MG, Vivanco F, Aranguez I, Somoza B, Segura J, Kreutz R, Fernández-Alfonso MS, Ruilope LM, Ruiz-Hurtado G. Clin Sci (Lond). 2016; 130(7):525-38

7. Genetic predisposition to albuminuria is associated with increased arterial stiffness: role of elastin. Gil-Ortega M, García-Prieto CF, Ruiz-Hurtado G, Steireif C, González MC, Schulz A, Kreutz R, Fernández-Alfonso MS, Arribas S, Somoza B. Br J Pharmacol. 2015;172:4406-18.

8. Arterial stiffness is associated with adipokine dysregulation in non-hypertensive obese mice. Gil-Ortega M, Martín-Ramos M, Arribas SM, González MC, Aránguez I, Ruiz-Gayo M, Somoza B, Fernández-Alfonso MS. Vascul Pharmacol. 2016;77:38-47.

9. Regional differences in perivascular adipose tissue impacting vascular homeostasis. Gil-Ortega M, Somoza B, Huang Y, Gollasch M, Fernández-Alfonso MS. Trends Endocrinol Metab. 2015;26:367-75.

10. Development of progressive albuminuria in male Munich Wistar Frömter rats is androgen dependent. Herlan L, Unland J, Langer S, Schulte L, Schütten S, García-Prieto CF, Kossmehl P, Fernández-Alfonso MS, Schulz A, Kreutz R. Physiol Genomics. 2015;47:281-9.

11. Vascular AMPK as an attractive target in the treatment of vascular complications of obesity. García-Prieto CF, Gil-Ortega M, Aránguez I, Ortiz-Besoain M, Somoza B, Fernández-Alfonso MS. Vascul Pharmacol. 2015;67-69:10-20.

12. Mild caloric restriction reduces blood pressure and activates endothelial AMPK-PI3K-Akt-eNOS pathway in obese Zucker rats. García-Prieto CF, Pulido-Olmo H, Ruiz-Hurtado G, Gil-Ortega M, Aranguez I, Rubio MA, Ruiz-Gayo M, Somoza B, Fernández-Alfonso MS. Vascul Pharmacol. 2015;65-66:3-12.

13. High-fat diet induces endothelial dysfunction through a down-regulation of the endothelial AMPK-PI3K-Akt-eNOS pathway. García-Prieto CF, Hernández-Nuño F, Rio DD, Ruiz-Hurtado G, Aránguez I, Ruiz-Gayo M, Somoza B, Fernández-Alfonso MS. Mol Nutr Food Res. 2015;59:520-32.

14. Development of albuminuria and enhancement of oxidative stress during chronic renin-angiotensin system suppression. Ruiz-Hurtado G, Condezo-Hoyos L, Pulido-Olmo H, Aranguez I, Del Carmen Gónzalez M, Arribas S, Cerezo C, Segura J, Praga M, Fernández-Alfonso MS, Ruilope LM. J Hypertens. 2014;32:2082-91.

15. Imbalance between pro and anti-oxidant mechanisms in perivascular adipose tissue aggravates long-term high-fat diet-derived endothelial dysfunction. Gil-Ortega M, Condezo-Hoyos L, García-Prieto CF, Arribas SM, González MC, Aranguez I, Ruiz-Gayo M, Somoza B, Fernández-Alfonso MS. PLoS One. 2014;9(4):e95312.

16. Dissecting the genetic predisposition to albuminuria and endothelial dysfunction in a genetic rat model. Steireif C, García-Prieto CF, Ruiz-Hurtado G, Pulido-Olmo H, Aranguez I, Gil-Ortega M, Somoza B, Schönfelder G, Schulz A, Fernández-Alfonso MS, Kreutz R. J Hypertens. 2013;31:2203-12;

17. Adaptative nitric oxide overproduction in perivascular adipose tissue during early diet-induced obesity. Gil-Ortega M, Stucchi P, Guzmán-Ruiz R, Cano V, Arribas S, González MC, Ruiz-Gayo M, Fernández-Alfonso MS, Somoza B. Endocrinology. 2010;151:3299-306.

18. Retaining perivascular tissue of human saphenous vein grafts protects against Dashwood MR, Savage K, Tsui JC, Dooley A, Shaw SG, Fernández Alfonso MS, Bodin L, Souza DS. J Thorac Cardiovasc Surg. 2009;138):334-40.

19. Comparative expression analysis of the renin-angiotensin system components between white and brown perivascular adipose tissue. Gálvez-Prieto B, Bolbrinker J, Stucchi P, de Las Heras AI, Merino B, Arribas S, Ruiz-Gayo M, Huber M, Wehland M, Kreutz R, Fernandez-Alfonso MS. J Endocrinol. 2008;197:55-64.

20. Perivascular adipose tissue and mesenteric vascular function in spontaneously hypertensive rats. Gálvez B, de Castro J, Herold D, Dubrovska G, Arribas S, González MC, Aranguez I, Luft FC, Ramos MP, Gollasch M, Fernández-Alfonso MS. Arterioscler Thromb Vasc Biol. 2006;26:1297-302.

Selected funded projects in the last 5 years

1. Title: Cross-talk between hypothalamic astrocytes and perivascular adipose tissue in energy metabolism and cardiovascular function: Impact of dietary modification. Funding: MINECO (BFU2017-82565-C2-2-R). Duration from 1.1.2018 to 31.12.2021. Principal investigator: Maria S. Fernández-Alfonso.

2. Title: Effect of finerenone on oxidative stress and vascular dysfunction in a rat model of spontaneous albuminuria (MWF rats). Funding Bayer AG. Duration from July 2015 – ongoing. Principal investigator: Maria S. Fernández-Alfonso.

3. Title: Influence of perivascular adipose tissue (PVAT) on the function of resistance arteries of obesity prone and resistant rats: mechanisms involved. Funding: MEC (BFU2011-25303). Duration from 1.1.2012 to 31.10.2015. Principal investigator: Maria S. Fernández-Alfonso.

4. Title: Identification of circulating microRNAs in hypertensive patients as markers of renal and cardiovascular damage associated to the presence of microalbuminuria. Funding: Fundación Mutua Madrileña. Duration from 1.10.2011 to 30.9.2014. Principal investigator: Gema Ruiz Hurtado

5. Title: Effect of aliskiren on energy metabolism in mice with diet-induced obesity. Funding: Novartis. Duration from 1.1.2011 31.12.2011. Principal investigator: Maria S. Fernández-Alfonso.

6. Title: Implication of the excess of perivascular adipose tissue in the development of vascular damage associated to obesity. Funding: MEC (SAF2008-02703). Duration from 1.1.2009 to 31.12.2011. Principal investigator: Maria S. Fernández-Alfonso.

Other

 PhD theses conducted: 11 (3 with European Mention and 2 in collaboration with Charite, Berlin).

 Total number of publications: 85. Of these, 71% in Q1 with 29% in D1

 Total citations: >1500;

 h-Index: 23