Proceedings of the Nutrition Society (2009), **67 (OCE7)**, E278 doi:10.1017/S0029665108009415

The challenge of translating nutrition research into public health nutrition, University College, Dublin, 18–20 June 2008

Obese IL-1 receptor-I-deficient (IL-1RI$^{-/-}$) mice are protected against diet-induced insulin resistance via a down-regulation of inflammation and oxidative stress in adipose tissue: a proteomics investigation

V. Rungapamestry[1], B. De Roos[2], K. Ross[2], G. Rucklidge[2], M. Reid[2], G. Horgan[3], S. Toomey[1], J. Browne[1], C. Loscher[1] and H. M. Roche[1]

[1]*Nutrigenomics Research Group, UCD Conway Institute, University College Dublin, Dublin 4, Republic of Ireland,* [2]*Division of Vascular Health and* [3]*Biomathematics and Statistics Scotland, Rowett Research Institute, Aberdeen AB21 9SB, UK*

In obesity the accumulation of white adipose tissue is associated with a chronic mild pro-inflammatory state characterised by enhanced secretion of inflammatory mediators by adipocytes and infiltration of macrophages in adipose tissue. This pro-inflammatory state has been implicated in the pathogenesis of insulin resistance and the development of type 2 diabetes mellitus[(1)].

IL-1 is secreted from stimulated macrophages and is involved in acute-phase inflammatory responses[(2)]. A proteomics approach has been used to explore the effect of modifying the inflammatory response on molecular markers of insulin sensitivity in transgenic mice on a high-fat diet. IL-1RI$^{-/-}$ male mice (n 7), which possess a compromised macrophage function, and C57BL/6J control mice (n 8) were challenged with a high-fat diet (60% energy from fat) for 16 weeks.

Despite an equal weight gain, IL-1RI$^{-/-}$ mice had lower plasma glucose ($P<0.0001$) and TAG ($P<0.01$) concentrations, and improved indices of insulin sensitivity, such as HOMA[(3)] ($P<0.01$) and revised quantitative insulin-sensitivity check index[(4)] ($P<0.0001$), compared with the control group. Proteomics analysis of epididymal adipose tissue (EAT) by two-dimensional gel electrophoresis and MS[(5)] indicated that 93 proteins, including post-translationally-modified isoforms, were significantly down regulated in IL-1RI$^{-/-}$, compared with control mice.

IL-1RI$^{-/-}$ mice had lower levels of the antioxidant proteins thioredoxin, peroxiredoxin, glutathione peroxidase, leukotriene A4 hydrolase, calcyclin protein and lysophospholipase, possibly indicating lower levels of reactive oxygen species in EAT compared with control mice. IL-1RI$^{-/-}$ mice also showed lower levels of various isoforms of proteasomes and ubiquitin ligase, which may suggest a down-regulation of the inflammatory response in EAT via decreased ubiquitination and proteasomal degradation of inhibitory subunit of NF-κB, and increased suppression of the key inflammatory transcription factor NF-κB. Furthermore, IL-1RI$^{-/-}$ mice had decreased expression of a host of cytoskeletal proteins, which may reflect apoptosis and cytoskeletal remodelling in EAT, possibly as a result of cell death of macrophages and monocytes. Correlation analysis of the proteomics data and plasma measurements suggested that decreased cellular stress may represent an important mechanism underlying improved insulin sensitivity in IL-1RI$^{-/-}$ mice.

These results show that disrupting components of the IL-1-mediated inflammatory response results in a marked protection from diet-induced insulin resistance, independent of obesity.

This study was funded by Science Foundation Ireland and by the Scottish Government Rural and Environment Research and Analysis Directorate.

1. Savage DB, Petersen KF & Shulman GI (2005) *Hypertension* **45**, 828–833.
2. Labow M, Shuster D, Zetterstrom M *et al*. (1997) *J Immunol* **159**, 2452–2461.
3. Matthews DR, Hosker JP, Rudenski AS, Naylor BA Treacher DF & Turner RC (1985) *Diabetologia* **28**, 412–419.
4. Perseghin G, Caumo A, Caloni M, Testolin G & Luzi L (2001) *J Clin Endocrinol Metab* **86**, 4776–4781.
5. de Roos B, Duivenvoorden I, Rucklidge G, Reid M, Ross K, Lamers RJ, Voshol PJ, Havekes LM & Teusink B (2005) *FASEB J* **19**, 813–815.