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Highlights

Oxidative stress and diabetes: Glucose response in the cROSSfire



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ABSTRACT

In this issue of the *Biomedical Journal*, we discuss the emerging role of reactive oxygen species (ROS) in the development of insulin resistance and ultimately type 2 diabetes. We focus also on research investigating the outcome of *in vitro* fertilization after laproscopic surgery for ovarian endometriosis. Finally, we learn the results of a study on the hunt for new probiotic bacteria.

Spotlight on reviews

Oxidative stress and diabetes: glucose response in the cROSSfire

According to the latest statistics from the World Health Organisation, 422 million people worldwide have diabetes [1]. The majority of these have type 2 diabetes, in which the body still produces insulin but cannot process it well. Understanding the mechanisms that lead to insulin resistance is essential for preventing type 2 diabetes. In this issue of the *Biomedical Journal*, Hurrell and Hsu [2] discuss the emerging role of oxidative stress in the development of insulin resistance, its link to obesity, and the therapeutic potential of antioxidants.

Reactive oxygen species (ROS) are a natural by-product of various metabolic processes and are produced at low levels during normal metabolism. As the name suggests, ROS are

highly reactive and remove electrons from anything in their path. Thus at above normal physiological levels, ROS cause damage to cells. To understand their role in insulin resistance, it is necessary to understand how peripheral tissues respond to insulin under physiological conditions. When blood sugar levels increase shortly after a meal, pancreatic beta cells secrete insulin into the bloodstream. Under normal conditions, peripheral tissues respond to insulin by increasing the expression of glucose transporters (particularly GLUT4) at the plasma membrane, thus opening the cellular flood gates to glucose. But if insulin levels are chronically high, GLUT4 expression is actually decreased [3]. This creates a strong positive feedback loop that ultimately results in insulin resistance. An important factor igniting and fuelling this loop is ROS. High insulin levels perturb signalling through NADPH oxidase 4 (NOX4), a powerful oxidizing enzyme that produces ROS. Through a series of downstream events [Fig. 1], high ROS levels set the trans-Golgi network on a course of whereby

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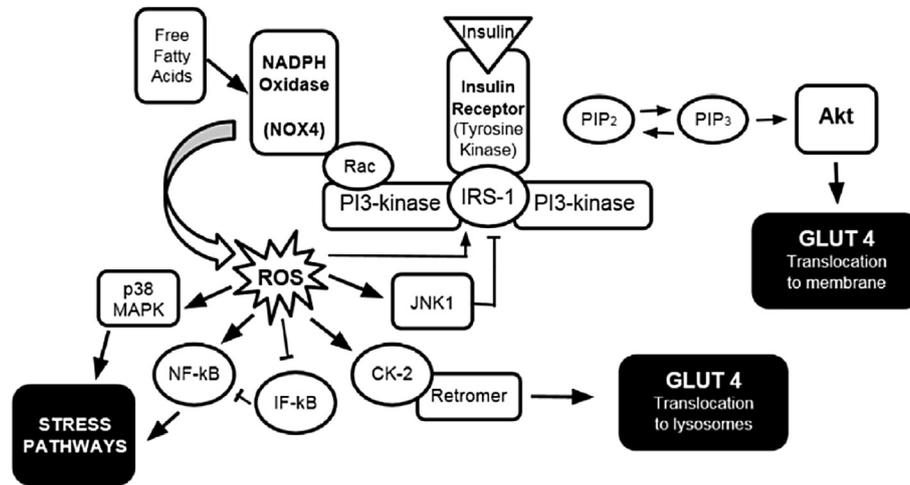


Fig. 1 How Reactive Oxygen Species contribute to insulin resistance. ROS contributes to insulin resistance by promoting the translocation of GLUT4 to lysosomes, as well as inducing various cellular stress pathway. This figure was kindly provided by Hurrell and Hsu [2] and the signalling pathways involved are described further in their review.

GLUT4 is transported to lysosomes for degradation instead of the plasma membrane [3].

In the context of a sugar rich diet and thus fuelled with plenty of substrate, mitochondria also contribute to high levels of ROS which cause damage to cells and set in motion a variety of stress responses. High ROS levels also lead to mitochondrial fission, which has been linked to insulin resistance in skeletal muscle [4]. A major known risk factor for type 2 diabetes, obesity, also contributes indirectly to mitochondrial dysfunction, likely through the high levels of circulating free fatty acids in individuals with obesity [5]. This dysfunction is reflected in the transcription of mitochondrial genes, which correlate with the degree of obesity [6]. Although many questions remain unanswered, for example about the timing of the events involved, it is likely that mitochondrial dysfunction is part of the complicated network of mechanisms linking obesity to type 2 diabetes.

If excess ROS and oxidative damage contribute to the development of insulin resistance, it follows that antioxidants that scavenge free radicals may help to prevent or combat type 2 diabetes. The antioxidant vitamins ascorbic acid (vitamin C) and tocopherol (vitamin E), as well as antioxidant flavonoid-containing compounds, have been extensively investigated with some promising results. In one randomized controlled trial, ascorbic acid supplementation increased insulin sensitivity of skeletal muscle in patients with type 2 diabetes [7]. Likewise, supplementation with anthocyanin, a water soluble flavonoid compound, improved dyslipidemia and insulin-mediated glucose disposal in type 2 diabetics [8]. However, many studies have failed to report clinically meaningful outcomes, and in excess, such supplementation may even be harmful [9]. These compounds are naturally present in many fruits and vegetables and there is no of course no better replacement for a balanced diet low in sugar.

Although current therapeutic use of antioxidants may seem disappointing, there is little doubt over importance that oxidative stress exerts over our health in general. Indeed, diabetes is just one of a multitude of diseases in which the uncontrolled production of ROS has been implicated [10].

Hopefully, concerted research efforts will identify novel targets or compounds that may prove to combat better the effects of ROS in insulin resistance.

Spotlight on original articles

Outcome of *in vitro* fertilisation after laproscopic surgery for endometriosis

Endometriosis is a common cause of infertility, and women treated for the condition and wanting biological children must, in most cases, undergo *in vitro* fertilisation (IVF). In this issue of the *Biomedical Journal*, Yu et al. [11] report promising news for women with bilateral ovarian endometriosis and treated by laproscopic surgery: when it comes to pregnancy outcome after IVF, two ovaries affected is no worse than one.

Around 10–20% of women of reproductive age have endometriosis [12], a condition in which tissues that normally line the uterus grow outside of it. In around one third of these cases, uterine tissues grow on one or both of the ovaries, giving rise to endometriotic cysts that can be removed by surgery. Laproscopic surgery is today the preferred method for the removal of endometriotic cysts, because it is minimally invasive and quicker than the open abdominal surgery. However, it requires a high level of training and skill on the part of the surgeon, who has the difficult challenge of distinguishing effectively between the cyst and normal ovarian tissue. With one study reporting that more than half of laproscopic cystectomies lead to loss of normal ovarian tissue [13], it follows that the success of subsequent IVF may be lower in women with two affected ovaries (bilateral endometrioma) than in those with only one affected ovary (unilateral endometrioma).

To investigate this question, Yu et al. [11] identified retrospectively 148 cycles of IVF performed in infertile women who had undergone laproscopic cystectomy for bilateral or unilateral endometrioma and compared ovarian response and

pregnancy outcome between the two groups. Controlling for various parameters such as age, BMI and duration of infertility, Yu and colleagues report that the number of oocytes retrieved and ultimately embryos transferred was lower in the bilateral group than in the unilateral group. However, these differences did not translate into differences in outcome, with the two groups showing similar rates of implantation, pregnancy and birth.

These findings are encouraging for women with bilateral endometrioma and are consistent with other reports in the literature showing that ultimately undergoing a bilateral cystectomy is no worse than undergoing a unilateral cystectomy in terms of pregnancy outcome [14]. Nonetheless, the experience of the surgeon cannot be overstated, with Yu and colleagues reporting previously that the experience of the surgeon who performed the laproscopic surgery influences ovarian reserve and subsequent birth rate after IVF [15]. Inexperienced surgeons have a greater risk of removing normal ovarian tissue. Thus, these current findings must await validation in a larger prospective study taking the experience of the surgeon into account.

Also in this issue

Review article

P2X4 in the limelight

In this review, Suurvali et al. [16] discuss the roles and properties of the purinergic P2X4 receptor. P2X4 is one of several receptors that recognizes extracellular ATP, but has been less widely studied than another receptor of this family: P2X7. Suurvali and colleagues present several convincing arguments for why this receptor should not be overlooked: it is 1000 times more sensitive than P2X7, it mediates neuropathic pain in a gender-specific manner, and through its ability to promote inflammation, it is linked to several diseases.

Original articles

Large Taiwanese clinical database under the spotlight

The Chang Gung Research Database (CGRD) is a de-identified database of medical records collected from the Chang Gung Memorial Hospital, the largest hospital system in Taiwan. With more than 280,000 patients admitted to the hospital system every year, the database is a gem for big data mining and has been used in around 1800 studies. However, the characteristics and coverage of the database with respect to the general population of Taiwan have never been studied before. Based on their analysis of nearly one million medical records from the CGRD, Tsai et al. [17] report that the severity of co-morbidities and the prevalence of certain diseases were higher in the CGRD than in the Taiwanese National Health Insurance Research Database. Thus, the CRGD could provide additional statistical power when studying complicated or rare diseases.

Fishing for probiotics

Over the past decade, *Lactobacillus* bacteria has gained much recognition for its reputed benefit for gastrointestinal health

[18]. This has led to a boom in the food industry of products containing *Lactobacillus*, which are frequently labelled “probiotic”. *Lactobacillus* are a natural component of the microbiota of humans and animals and are particularly enriched in dairy products. In an attempt to identify new *Lactobacillus* strains with probiotic activity, Prabhurajeshwar et al. [19] isolated *Lactobacillus* from local homemade and commercially available dairy products and tested their *in vitro* antimicrobial activities against pathogens. Their work identifies three promising strains of probiotic bacteria for validation *in vivo*.

Tuberculosis lymphadenitis on the decline in Eastern India

India has the highest burden of tuberculosis (TB) worldwide, accounting for 2.2 million of the 9.6 million cases reported globally in 2015 [20]. Fortunately, both the overall rate of and mortality from tuberculosis in India are declining, but in some regions there is relatively scarce information on the occurrence of TB lymphadenitis, a chronic granulomatous inflammation of the lymph node that is commonly associated with the disease. Dasgupta et al. [21] investigate trends of TB lymphadenitis in Eastern India and report encouragingly that the occurrence of TB lymphadenitis has decreased over the past ten years in the region.

Improving patient care through clinical audits

The past few decades have seen significant improvement to equipment, techniques and pre- and post-operative care. Despite the continuing introduction of such improvements, clinical audits to assess mortality rates over time remain an essential tool for a functioning health care system. In this retrospective study, Kumar et al. [22] carry out the equivalent of assess 5-year trend in the mortality rate in the otorhinolaryngology ward of a tertiary care centre in urban India, to identify trends in mortality and serve as the basis for improving patient care even further.

Conflicts of interest

The author declares no conflicts of interest.

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