Resveratrol: Challenges in translating pre-clinical findings to improved patient outcomes

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Editorial

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In recent decades, the average life expectancy of humans, particularly in westernized societies, has been steadily increasing. Better nutrition and health care are among the factors responsible for the increased lifespan. However, although life expectancy is increasing, the prevalence of chronic diseases is also rapidly increasing. For example, obesity is becoming a major health problem in a large part of the world, and countries with greater than 50% of the adult population being overweight are becoming the norm. This increase in the prevalence of obesity comes with a further increase in chronic metabolic diseases, which threatens the steady increase in life expectancy that we have grown accustomed to. Therefore, research efforts are shifting towards attempts to prolong a healthy life by reducing the prevalence of obesity as well as attempts to develop novel therapies that maintain normal metabolism even in the presence of obesity. One of these therapies, resveratrol, has been shown in animal models and in a few clinical studies to have benefit in patients with metabolic conditions arising from obesity and/or insulin resistance. In addition, resveratrol also appears to hold promise for the treatment of many chronic diseases both dependent and independent of changes in metabolism.

Interest in resveratrol expanded after it was identified as an active polyphenol, present in higher amounts in red wine, which could have cardioprotective by inhibiting platelet aggregation and lowering low-density lipoprotein levels. Subsequent investigation of the pharmacological activities of resveratrol revealed that it also has potent antioxidant, anti-carcinogenic and anti-inflammatory activities. Furthermore, in 2003 resveratrol was discovered to be a small molecule activator of SIRT1, a molecule that has been linked to longevity. In the years that followed, resveratrol has been extensively studied in cell and animal studies, in a wide range of diseases. In fact, a PubMed search with 'resveratrol' as a keyword reveals over 7000 publications, demonstrating the vast amount of research being conducted in order to describe and understand the effects of resveratrol. Of importance, resveratrol has been linked to beneficial effects not only in obesity and energy metabolism, but also in cardiovascular disease, cancer, osteoporosis, neurological disorders, Alzheimer's, as well as extending lifespan.

Overall, the results of the pre-clinical studies have been promising and these findings have created high expectations for the therapeutic value of resveratrol to treat chronic diseases. However, as is often the case, the translational steps from cell and animal studies towards humans has turned out to be less than straightforward. Although the number of clinical trials with resveratrol is still limited (combining the PubMed search 'resveratrol' with 'clinical trial' only reveal ~80 publications — of which many are reviews), the number of trials showing beneficial effects may balance the number of trials that failed to show favourable effects. This then begs the question: does this mark the end of resveratrol as a promising candidate to improve health in humans? Before this question can be answered, many other questions need to be answered first. For example, do we know what the optimal dose and treatment duration for resveratrol is, and have we fully revealed its exact mechanism(s) of action? Furthermore, it needs to be revealed for which subjects/patients resveratrol may be beneficial, as it may be too simplified to assume that it will improve health in all (patient) populations spanning a vast array of conditions. Thus, more well-designed clinical trials are needed before we can decide whether or not resveratrol can meet our high expectations.

The goal of this special issue is to provide detailed reviews of the existing literature covering a wide breadth of topics and to help address the challenges associated with translating the pre-clinical data to humans. As we contemplate the existing findings, it may be good to reset the expectations of resveratrol, as it may be unrealistic to consider resveratrol as a wonder drug that can relieve all negative consequences of our lifestyle characterized by nutritional overconsumption, physical inactivity, and other stresses.

Dr. Jason Dyck is a Professor in the Department of Pediatrics and the Director of the Cardiovascular Research Centre at the University of Alberta. He is also the co-director of the Alberta HEART, which is a program aimed at understanding and treating heart failure. Dr. Dyck has a broad area of research that includes the study of obesity, insulin resistance, diabetic cardiomyopathy, chemotherapy-induced cardiotoxicity, ischemia/reperfusion injury, hypertension and heart failure. These diverse research topics are linked by Dr. Dyck's interest in how alterations in energy metabolism contribute to these conditions as well as the effects of resveratrol as a treatment strategy.

Dr. Patrick Schrauwen is a Professor in the Departments of Human Biology and Human Movement Sciences at the Maastricht University Medical Center. Dr. Schrauwen's main fields of interest in research concern muscular insulin resistance, lipotoxicity and mitochondrial dysfunction with special emphasis on type 2 diabetes mellitus. The research team supervised by Prof. Schrauwen investigates whole-body, tissue and cellular physiology. To this end, molecular, genetic and whole-body techniques are used in both rodent and human models. In collaboration with the Department of Radiology of the Maastricht University Hospital, Prof. Schrauwen applies non-invasive magnetic resonance spectroscopy to investigate in vivo mitochondrial function and lipid accumulation in the muscle, liver and heart. Dr. Schrauwen is investigating if targeting mitochondrial function, among others via resveratrol, can aid to prevent and treat type 2 diabetes and its related complications.

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