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COMMENTARY

Is *PPARG* the key gene in diabetic retinopathy?

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Diabetic retinopathy, a microvascular complication of diabetes mellitus, is major cause of non-inherited blindness among adults. Although diabetic retinopathy is a common complication of diabetes, we still know little about the underlying molecular mechanisms. In recent years, complex connections between important molecules and pathways in the onset and progression of diabetic retinopathy, such as advanced glycation end products, oxidative stress and inflammation, have been elucidated. Biochemical, genetic and functional studies strongly indicate peroxisome proliferator-activated receptor-γ (PPARγ), a pleiotropic transcription factor, as a primary target in the treatment of diabetic retinopathy. In this issue, Song *et al.* detail the role of PPARγ in diabetic retinopathy-related disorders, illustrating PPARγ-mediated inhibition of diabetes-induced leukostasis and leakage, and its beneficial role in modulating inflammation, angiogenesis and apoptosis in retinal and endothelial cells. Moreover, they describe alternative treatments for diabetic retinopathy, such as plant-derived PPARγ ligands, proposing their use – in combination with standard therapies – for modulation of diabetic retinopathy.

LINKED ARTICLE

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Abbreviations

PPARG, gene encoding peroxisome proliferator-activated receptor-γ; PPARγ, peroxisome proliferator-activated receptor-γ; TCM, traditional Chinese medicines

Diabetic retinopathy is a severe microvascular complication of diabetes mellitus, which occurs within in the first two decades from diabetes onset. It affects the retina of almost all patients with type I diabetes and about 60% of those with type II diabetes. Changes in the retinal biochemistry and physiology appear long before clinically evident disease is observed. Furthermore, characteristic symptoms, such as macular oedema, vitreous haemorrhage, traction retinal detachment, exudates and intraocular pathological neovascularization, are observed in nearly all patients, even with variable severity (Silva *et al.*, 2010). All the mechanisms underlying diabetic retinopathy, as for other vascular complications of diabetes mellitus, have not yet been fully elucidated. However, in the last years the complex relationship existing among the most relevant contributors to the onset and progression of diabetic retinopathy, such as advanced glycation end products, oxidative stress, inflammation and angiogenesis, have been intensively investigated and, particularly, by whole-genome expression analyses in cells and animal models (Brucklacher *et al.*, 2008). Moreover, gene expression profiling of altered genes in animal models of diabetic retinopathy has provided novel intriguing molecular targets to be validated through focused studies, which can be useful to improve our knowledge of retinal physiology and pathophysiology, in conditions such as diabetes mellitus. The data from this gene expression profiling reinforce the hypothesis of a feed-forward cycle of chronic inflammation and neurodegeneration (Brucklacher *et al.*, 2008).

In the light of the complex interactions among the different molecular pathways in the retinal (different subtypes of retinal cells) and endothelial cells, it is not easy to fully exploit the real contribution of each factor to the pathogenesis of diabetic retinopathy, and particularly to address the potential targets for a drug-based therapeutic approach.

However, recent studies on patients with diabetic retinopathy and appropriate animal models have shown that the

gene, *PPARG*, encoding a member of the nuclear receptor superfamily, the peroxisome proliferator-activated receptor-γ (PPARγ), may represent a valuable target to rescue – or ameliorate – the endothelial and retinal damage due to high-glucose-induced prolonged inflammation (Gerry and Pascual, 2008).

The protein PPARγ is a ligand-inducible pleiotropic transcription factor, which has different isoforms characterized by distinct expression patterns and functions (Sabatino *et al.*, 2005). This transcription factor is able to modulate its transcriptional activity through conformational changes and the binding to different – temporally and spatially regulated – cofactors (Perissi and Rosenfeld, 2005). Furthermore, non-canonical mechanisms, such as SUMOylation of PPARγ ligand-binding domains, are responsible for the repression of inflammatory response genes controlled by NF-κB (Pascual *et al.*, 2005). Nevertheless, its activation by natural or synthetic ligands may also provide undesirable and often unexplained side effects, which are directly linked to its functioning as regulator of gene expression with (potentially) opposite effects in different cells, tissues or organs, according to the specific surrounding environment (Costa *et al.*, 2010).

Moreover, key roles for PPARγ in glucose metabolism, angiogenesis and inflammation pathways, the growing evidence of the anti-inflammatory, -oxidative and -proliferative effects of its synthetic and natural ligands (Knouff and Auwerx, 2004), and also the association of nucleotide variants in the *PPARG* gene with diabetes mellitus and with diabetic retinopathy (Malecki *et al.*, 2008; Costa *et al.*, 2009), all strongly suggest that this nuclear receptor should be a primary target in treatment of diabetic retinopathy.

In this issue of the *BJP*, Tom Huang's group (Song *et al.*, 2011) highlight, for the first time, in a comprehensive review article, the key role of *PPARG* in diabetic retinopathy-related disorders. As the pathogenesis of diabetic retinopathy involves different complementary molecular mechanisms, the authors describe in detail the complex connections between the pathways involved and the related protein effectors, citing most of the relevant work in the field. In addition, the PPARγ-mediated inhibition of diabetes-induced retinal leukostasis and leakage, and the role of this nuclear receptor within apoptosis, inflammation and angiogenesis pathways, are also clearly elucidated. Moreover, Song *et al.* provide a full description of PPARγ ligands derived from medicinal plants and they explain the potential of using these compounds in the modulation of diabetic retinopathy-related pathogenesis. Indeed, in the last years, there has been a growing interest in this area and some important results have emerged in the use of alternative therapies, such as traditional Chinese medicines (TCM) and the therapeutic use of natural compounds, especially those derived from plants.

Novel treatments, derived from natural sources, possibly in combination with commonly used 'standard therapies', may help to provide major improvements in efficacy and in safety profiles for these treatments and/or the prevention of diabetes mellitus and its related microvascular and macrovascular complications, including diabetic retinopathy. However, as underlined by Song *et al.*, there are few and not yet conclusive, studies on the efficacy and safety of treatments based on natural and herbal medicines, although their use in medical practice has become wider, in the last few years. Furthermore, although there are many individual examples of the successful clinical use of these non-traditional herbal formulations, to date no registered clinical trials for treatment of diabetic retinopathy are currently active (except 'NCT00904592' for TCM, http://www.clinicaltrials.gov). Systematic analyses, from both clinical and basic research, are still in their infancy and much more effort is needed in this direction. Indeed, the direct effects of the phytochemical components – contained in these herbal formulations – on the molecular pathways of cells and/or animal models have not yet been systematically addressed, thus impairing, or at least putting in doubt, their potentially scientific validity. Nonetheless, very recently, systematic approaches – mostly relying on hybridization-based technology – have been used for elucidating the molecular targets of TCM and their mechanisms of action (Kang *et al.*, 2005; Wang *et al.*, 2008; Wen *et al.*, 2011). These findings have indicated that the study of gene expression changes may represent a powerful tool to understand the mechanisms of actions for several natural compounds in different cell models. By combining together – and integrating – genomics, proteomics and metabolomics data, putative novel biomarkers are likely to be identified, allowing also the assessment of the quality of herbal formulations (Wen *et al.*, 2011). Moreover, a thorough and systematic examination of changes in gene expression induced by herbal formulations is likely to be a crucial task.

Finally, extensive preclinical and clinical trials, driven by a detailed and proven knowledge of the molecular targets, are needed to establish the efficacy and to prove the safety of many commercially available natural medicines, possibly in combination with standard therapy, for the treatment of diabetic retinopathy and for other vascular complications of diabetes.

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