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Antioxidant synthetic peptides counteracting hyperglycaemia induced endothelial cell dysfunction

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In the issue of International Journal of Cardiology, Hemling P. et al. describe the impairment of thioredoxin (TRX) activity is partially responsible for reactive oxygen species (ROS) accumulation in hyperglycaemic endothelial cells (EC). Interestingly, authors extend this finding to placental arterial EC where the employment of TRX synthetic peptides is able to restore physiological levels of ROS and subsequent improvement of the VEGF-A response, which is diminished in diabetic conditions [1]. The article sheds light on the biological impact of TRX-based as a link between the redox systems and endothelial function in hyperglycaemia. Few papers focus on the role of TRX in association to diabetic impaired angiogenesis. Trx role in angiogenesis is established, where Trx is a redox reactive protein associated to a broad spectrum of biological activities and influencing angiogenesis processes such as cell proliferation and migration, reduction of apoptosis, and modification of molecular targets including HIF-1α, p53 and nrf2 [2]. Both TRX isoforms 1 and 2 have been reported as protective for the cardiovascular system, strengthening the role of the redox balance in the endothelial system. Nevertheless, novel studies are also emerging on the significance role exerted by thioredoxin-binding protein (TRXBP/TXNIP), the endogenous and negative regulator peptide of TRX. Due to a regulating region of the promoter responsive to carbohydrate, the expression of TRXBP/TXNIP is upregulated in diabetic conditions and especially in β-pancreatic cells [3]. Hyperglycaemia exacerbates the interaction between TRX and TRXBP. Insulin levels are downregulated by TRXBP/TXNIP trough miR204/MafA pathway [4], resulting in dysfunctional pancreatic cells. Although Hemling et al., have ruled out a mechanistic in vitro role of TRXBP/TXNIP in mediating the improved angiogenic effects of TRX mimetic peptides upon hyperglycaemia, the clinical importance of the TRXBP should still be considered in vivo. For instance, both hypoglycaemic and hypertensive drugs routinely administered to patients such as insulin, calcium channels blockers, and metformin [5] are able to pharmacologically modulate the TRXBP with promising clinical results, therefore strengthening the concept that the TRX/TRXBP complex might represent an interesting “anti-redox system”, a crossroads between diabetic and cardiovascular complications. From a further standpoint, the link between oxidative stress and diabetes is largely acknowledged. Reactive oxygen species, generated by the combination of concomitantly altered biochemical pathways and epigenetic mechanisms, have a role in determining the biological dysregulation of the micro and macrovasculature of the vessel bed, mainly affecting the cardiovascular system and causing the

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functional organ failure in affected subjects [6]. Diabetes enhances cellular oxidative stress, although the source of increased ROS is debated, it is likely to originate from various sources including dysregulated antioxidant systems, mitochondria or glycated products [6]. Advances in antioxidant therapies has been hampered by the inability of antioxidants to have clinical efficacy. To date, the question remains: if the oxidative sensor is imbalanced in diabetic conditions, is it conceivable to restore the overall physiological levels of ROS by removing toxic oxidative products in patients? Or alternatively, could targeting of defined molecules/pathways represent a better strategy to tackle endothelial dysfunction in diabetes? In this latter perspective the article by Hemling et al. is contextualized. Interestingly, when EC are subjected to a supra-pathophysiological level of glucose and glucose metabolite (hyperglycaemia cocktail), TRX levels were decreased likely exasperating the effect of ROS. Care should be taken in interpretation of the results. Trx deficiency directly promoted ROS activity was not proven in these data. Treatment with the hyperglycaemia cocktail may induce ROS in endothelial cells, which could be mimicked by TRX depletion however there could be multiple sources of elevated ROS. Changes in expression or activity of other antioxidant or oxidant proteins were not investigated. Secondly, a question lies with the specificity of Trx mimetics and pharmacological inhibition. The different isoforms have specific actions and subcellular localisation whereas the study did not distinguish between inhibition or mimicking isoform location. Synthesis of new peptides appropriately designed to correct the redox imbalance might represent a novel frontier to integrate and to replace a more general and univocal antioxidant-based therapy, but selectivity would need to be carefully considered TRX deficiency has the potential to effect lowering of angiogenesis in diabetics through a broad range of cellular activities. TRX is likely to exert its effect through modification of cysteines on key proteins inducing changes in oxidative post-translational modification. The article by Hemling et al. have provided clues for identification of these proteins by highlighting the potential biological pathway such as migration, proliferation and/or apoptosis as key to the changes in endothelial cell function observed. Another aspect of the article by Hemling et al which needs further exploration is the lowering of VEGFR2 cell surface expression in diabetic treated cells. VEGFR2 undergoes endosome-to-plasma membrane recycling after ligand binding limits receptor activity. In addition to cell membrane expression it remains to be seen if TRX mimetics are able to restore VEGF signalling including VEGFR2 phosphorylation and subsequent activation of downstream pathways. Lastly this article investigated TRX mimetic treatment in gestational diabetic patients, a higher risk set of subjects with pronounced cardiovascular complications. TRX also plays a key role in reproduction and pregnancy. Human trophoblasts cells are able to secrete the extracellular form of TRX and therefore to counteract the detrimental effects of oxidative stress by interacting with the cytokine network at the fetomaternal interface [7]. In the first trimester of pregnancy, when placenta develops in a low oxygen environment is prevalent, parallel high expression of TRX and ROS in both stromal and endothelial compartment of placenta is observed. Studies on preeclampsia, a classic dysregulated inflammatory and oxidative disorder of pregnancy, have shown that the TRXBP activation targets the NLP3 inflammasome and IL-β, revealing as an antioxidant molecule can act as regulator of the immune response [8]. In pregestational diabetes the TRXBP/TRX complex assumes clinical significance, as it is negatively modulated by increased levels of miRNA-17 induced by hyperglycaemia, and leading to the activation of the apoptosis signal-regulating-Kinase 1 (ASK-1) and neural tube defects at birth [9]. Consistently, the TRX/TRXBP ratio in gestational diabetes has been described higher than controls, suggesting its functional, active and compensating role of physiological antioxidant [10]. In diabetic conditions therapeutic angiogenesis by means of antioxidant targets is emerging. The future management of the restoration of the physiological balance of ROS should be designed according to the pathophysiological heterogeneity of diabetes among tissues and with a more personalized and targeted approach for specific sets of patients.

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