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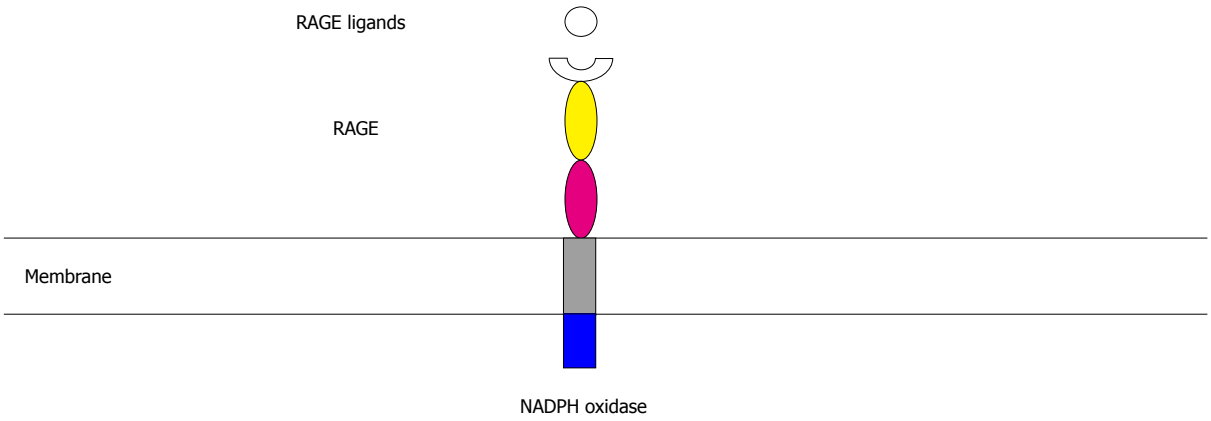

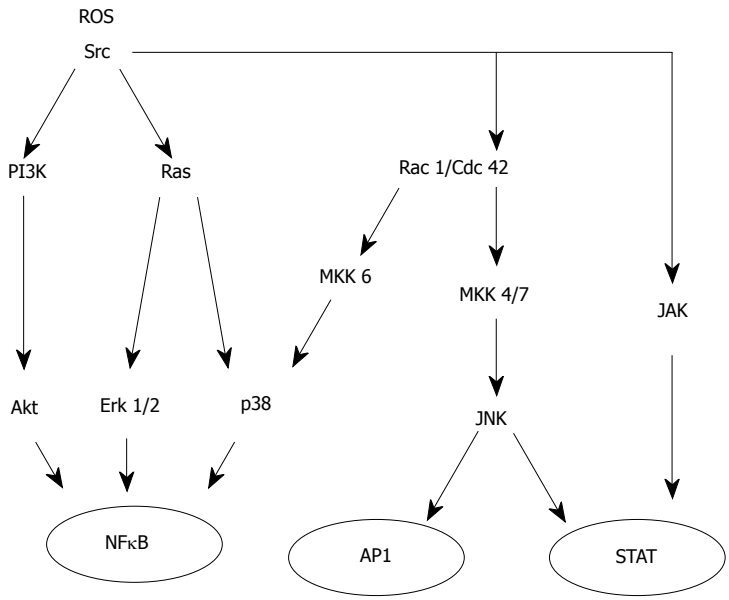

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EDITORIAL

Complexity of drug therapy and its implications for quality of diabetes care

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Abstract

Diabetes is a leading cause of mortality, morbidity and disability around the globe. In the past two decades, diabetes care has grown more complex as patients have received multi-component care. Recent studies have illumined the complexity of drug therapy in patients with diabetes. A high level of drug utilization in diabetes patients has serious implications for quality of care, in terms of coordination of care, drug safety and access to care. Practitioners, researchers, payers and policy makers should be aware of these implications and incorporate the complexity of diabetes care into practice guidelines, benefit design and policy formulation to improve the quality of care.

Key words: Complexity; Drug therapy; Quality of care

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INTRODUCTION

Diabetes is a leading cause of mortality, morbidity and disability around the globe. In the United States alone, 25.8 million adults and children (8.3% of the population) have diabetes, and a further 79 million adults (1/3 of the adult population) have pre-diabetes. Diabetes contributed to 231 404 deaths in 2007 and diabetes care cost $174 billion in 2010 in the US[1]. According to earlier research, diabetes ranks as the 8th most costly condition in financial terms, 2nd in causing impairement of the activities of daily life (ADL)/instrumental activities of daily life (IADL), 3rd in hospital bed days, and 8th in work-loss days in the US[2]

DATA AND ANALYSIS

Diabetes is a progressive condition. As the disease progresses, patients are frequently diagnosed with chronic complications including cardiovascular disease, nephropathy, dyslipidemia, coronary heart disease, retinopathy, and neuropathy. Even more concerning is that newly diagnosed diabetes patients are often found to have signs of these complications[3]. The position statement by the American Diabetes Association recommends a variety of medications for those complications. These include, *angiotensin-converting enzyme inhibitors (*ACE inhibitor) or angiotensin receptor blockers (ARBs) to treat cardiovascular disease and nephropathy, statins for dyslipidemia, aspirin for those at increased cardiovascular risk, and β-blocker to treat coronary artery disease[4]. Studies have also reported increased risk of cancers at multiple sites in diabetes patients although the link remains unknown. Some authors have suggested that

cancer should be considered as one complication of diabetes. As their diabetes progresses, patients take more and more drugs concurrently to prevent or treat these complications.

A study on the trends in complexity of diabetes care in the United States indicated that during the decade from 1991 to 2000, the standard of care for diabetes mellitus evolved to require more intensive management of glycemia, blood pressure and cholesterol level[5]. Another study on the complexity of medication regimen and test ordering suggested that from 1995 to 2003, diabetes care grew more complex. The largest change was in the number of patients receiving multi-component of diabetes care as the percentage of patients on cholesterol lowering drugs, blood pressure lowering drugs, and the percentage of patients receiving cholesterol and urine microalbumin tests all increased significantly[6].

A recent study further illumined the complexity of drug therapy in patients with diabetes. The study was based upon 2189 adult diabetes patients, comprising a nationally representative sample of 17.5 million diabetes patients in the US. The study found that a total of $56.1 billion was spent on prescription drugs by diabetes patients in the US in 2006. In 2006, each diabetes patient had an average of 46 prescriptions, totaling $3161 of drug expenditure, including $1061 out-of-pocket expenditure. The top 5 drug classes were antidiabetic agents (24.1% of total drug spending), lipid lowering drugs (13.4%), analgesics (4.4%), proton pump inhibitors (3.8%) and ACE inhibitors (3.7%). On average a diabetes patient used 3.52 (standard deviation = 1.76) classes of drugs within the 10 drug classes with the highest utilization[7].

DISCUSSION

The high level of drug utilization in diabetes patients has serious implications for quality of care. The uppermost concern is the coordination of care. Diabetes patients are cared by and referred to a number of physicians with different specialties. For example, in addition to visiting primary care physicians, they may also rely on care from endocrinologists and cardiologists. Previous research has suggested different treatment patterns among those specialties, and specialty care plays a critical role in caring for diabetes patients[8]. Thus, further research is warranted on a model to guide patients through the complex care system which may be fragmented and can result in serious conflicting treatment priorities. The research development model of a medical home, aligning the traditional gatekeeping role of primary physicians and a set of care settings, may be promising in this respect.

Another key concern arising from the complexity of drug therapy in diabetes patients is drug safety. Since diabetes patients are taking many drugs for diabetic complications and other acute conditions concurrently, there is a significant risk for drug-drug interactions. Despite the high risk of drug interactions in elderly patients, the prevalence of these interactions is not well documented[9]. In addition, reports suggest that patients are increasingly using herbal medicines, whose safety and efficacy are not well understood. Furthermore, patients often take those herbal medicines without the knowledge by their primary care physicians. There is an urgent need to study the safety issues which impact the various drug therapies of diabetes patients, and to discern and develop systematic ways to improve patient safety.

A third major concern regarding the complexity of drug therapy for diabetes patients is the access to pharmacotherapy. While in recent decades there has been a substantial improvement in insurance benefit design around the globe, particularly in the US, out-of-pocket payments for prescription drugs, particularly the newer, more expensive brand-name drugs, remains a concern. Because diabetes patients purchase a large number of prescription drugs and they are often significantly constrained by their economic means due to disability and advanced age, research to investigate affordability and access to multiple lines of drug therapy for these patients is much needed.

Last but not least, the role of regulatory authorities in approving and discrediting drugs warrants careful examination. In the case of rosiglitazone, studies have found that it was associated with increased risk of heart attack in diabetes patients. However, although it was suspended by European Medicines Agency, it was allowed to remain in the market by the US FDA. The development of a surveillance system on drug safety at the national level and quick actions by regulatory agencies would greatly facilitate data collection and improve patient safety.

CONCLUSION

In summary, the implications of the complexity of drug therapy on quality of care for diabetes patients cross the boundaries between specialty care, drug safety, and health benefit design. It is likely that these issues are interrelated. For example, an insurance plan may mandate a gatekeeping primary care physician and, as a result, referral arrangements for specialty care can be better coordinated. Research is much needed to investigate the comparative effectiveness of various care models to improve the overall well-being of diabetes patients.

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GUIDELINES FOR BASIC RESEARCH

Diabetes and cancer: Looking at the multiligand/RAGE axis

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Abstract

The association between diabetes and hyperglycemia and the associated increased risk of several solid and hematologic malignancies has been the subject of investigation for many years. Although the association is not fully understood, current knowledge clearly indicates that diabetes may influence malignant cell transformation by several mechanisms, including hyperinsulinemia, hyperglycemia and chronic inflammation. In this context, the receptor for advanced glycation end-products (RAGE) has emerged as a focal point in its contribution to malignant transformation and tumor growth. We highlight how RAGE, once activated, as it manifests itself in conditions such as diabetes or hyperglycemia, is able to continuously bring about an inflammatory milieu, thus supporting the contribution of chronic inflammation to the development of malignancies.

Key words: Diabetes; Cancer; Inflammation; Receptor for advanced glycation end-products; Malignant transformation

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INTRODUCTION

The association between diabetes and hyperglycemia and cancer, has been investigated extensively. Most studies, but not all, have found that both conditions are associated with an increased risk of several solid and hematologic malignancies. Currently, more than 250 million people live with diabetes; hence any impact derived even in smaller increases in the risk of cancer may have important consequences at world population level, and on associated costs to healthcare systems worldwide[1]. Although this association has been consistently reported for the most common cancer, more research efforts are needed, particularly in connection with the less common cancers, where data are limited or absent[2].

From the biological point of view, an essential question is raised when the association is analyzed: What are the mechanistic links between diabetes and cancer risk? Obviously, the answer to this question is not easy to find. However, and based on current knowledge, diabetes may influence malignant cell transformation by several mechanisms, including hyperinsulinemia, hyperglycemia and chronic inflammation. These three mechanisms are closely related to the receptor for advanced glycation end-products (RAGE), which may represent a focal point in their respective contri-

butions to malignant transformation.

In 1927, Otto Warburg and co-workers reported the increased uptake of glucose and production of lactate by tumors. At present, resurgent research interest in the Warburg effect, as it is now known, have brought about a growing body of evidence supporting the dependence of many tumors on glycolysis for energy production. One consequence of the rise of glycolysis is the non-enzymatic glycation of proteins, leading to the formation of advanced glycation end-products (AGEs)[3,4]. AGEs were the first identified RAGE ligands, particularly N-carboxymethyllysine [CML]-modified proteins[5].

The formation of AGEs is based on the non-enzymatic reaction of the reactive aldehyde moiety of glucose with the amino groups of proteins, forming slowly reversible Amadori products. Rearrangement reactions then occur to produce a chemically related group of moieties, termed AGEs, which remain irreversibly bound to proteins[6].

The major AGEs *in vivo* appear to be formed from highly reactive intermediate carbonyl groups, known as α-dicarbonyls or oxoaldehydes, including 3-deoxyglucosone, glyoxal, and methylglyoxal[7,8].

There is considerable evidence linking hyperglycemia with the accelerated formation of irreversible AGEs, which subsequently accumulate in different tissue locations[9,10,11]. Of note, the presence of AGEs has been detected in human cancer tissues, and their expression is markedly varied between different types of tumors[12].

It has been demonstrated by different authors that the circulating level of AGEs is associated with insulin resistance even in non-obese, non-diabetic subjects, independent of adiponectin levels[13,14,15].

How AGEs can impact insulin actions has been recently reviewed by Schalkwijk and co-workers[16]. Experimental data, obtained from both animal and isolated muscle and adipose tissue, suggest that glycation of insulin significantly impairs its biological activity[17].

It is also known that the increase of endogenous methylglyoxal accumulation impairs the insulin-signaling pathway and decreases insulin-stimulated glucose uptake in adipose tissue, which, in turn, may contribute to the development of insulin resistance[18,19].

Reduced intake of dietary AGEs has been shown to decrease the incidence of type 1 diabetes in non-obese diabetic mice[20], as well as the formation of atherosclerotic lesions in diabetic apolipoprotein E-deficient mice[21]. Vlassara and co-workers[22] have also shown that reduced AGE intake leads to lower levels of circulating AGEs and to improved insulin sensitivity in *db/db* mice. Furthermore, AGEs are reported to impair insulin action in muscle tissue by the formation of a multi-molecular complex, including RAGE/IRS-1/Src and PKCα[23].

RECEPTOR FOR ADVANCED GLYCATION END-PRODUCTS

The receptor for advanced glycation end-products (RAGE) is a member of the immunoglobulin protein family of cell surface molecules[24] and shares structural homology with other immunoglobulin-like receptors. Firstly described in 1992, RAGE has attracted increasing attention, due to its diverse ligand repertoire and its involvement in several pathophysiological processes associated with inflammation, such as diabetes, cancer, renal and heart failure, as well as neurodegenerative diseases[25,26].

The RAGE gene is localized on chromosome 6 in the vicinity of the MHC class Ⅲ complex region in humans and mice, and in close proximity to the homeobox gene HOX12 and the human counterpart of the mouse mammary tumor gene int-3[27,28].

RAGE is highly expressed during development, especially in the brain, but its expression level decreases in adult tissues. However, RAGE expression is also markedly augmented by increased levels of ligands, as observed in some pathologic states[29]. The mature 382 amino-acid long RAGE is composed of an extracellular domain (85 aa), a single transmembrane spanning helix (27 aa) and a short cytosolic region (41 aa)[30]. The extracellular domain of RAGE contains one variable, like V-domain, and two constants, like C type domains, which are frequently referred to as C1 and C2 domains. Recent studies suggest that RAGE forms oligomers at the cell surface[31]. RAGE possesses two N-glycosylation sites, one adjacent to the V-domain and the second one located within the V-domain[32].

Recently, RAGE splice variants have been classified and renamed according to the Human Gene Nomenclature Committee[33], and many of them appear to be more abundant under various pathological conditions. At DNA level, the RAGE gene consists of 11 introns/exons that can alternatively be spliced into different variants. In terms of prevalence, the three major isoforms appear to be the full-length RAGE, a secreted form RAGE_v1 (previously named as sRAGE, secretory C-truncated RAGE, esRAGE, hRAGEsec or sRAGE1/2/3) and a N-terminally truncated isoform RAGE_v2 (previously named Nt-RAGE, N-RAGE or N-truncated RAGE). It is important to point out that RAGE_v1 is released into the extracellular compartment, where it can interact with free RAGE ligands, then working as a "decoy receptor", thereby preventing ligands from interacting with cell surface RAGE[34].

RAGE AS A MULTILIGAND RECEPTOR

In addition to AGEs, other molecules have been identified as RAGE ligands, as has been demonstrated for S100/calgranulins; high-mobility group box 1 (HMGB1) have also been identified as ligands of this promiscuous receptor. The S100/calgranulin protein family comprises several members of non-ubiquitous Ca-binding proteins of the EF-hand type that have both intracellular and extracellular functions. At intracellular level, S100 proteins are responsible for different roles in the cell cycle, cell differentiation and cell motility. However, some members of the family have additional relevant extracellular roles, particularly

at sites of chronic inflammation, where they are able to activate, *via* RAGE, endothelial cells, macrophages and peripheral blood mononuclear cells, including T lymphocytes[35].

The DNA binding protein HMGB1 stabilizes nucleosome function, and acts as a transcription factor that regulates the expression of several genes[36]. HMGB1 belongs to the so-called "damage associated molecular pattern molecules" or alarmins, which are released in response to infection or inflammatory stimuli, especially during tissue damage[37].

Although glucose may be the triggering stimulus to draw RAGE into diabetes pathology, consequent cellular stress results in the release of pro-inflammatory RAGE ligands S100/calgranulins and HMGB1. Thus, RAGE engagement in diabetic tissue produces a vicious cycle of ligand-RAGE perturbation, leading not only to chronic tissue injury, but also suppression of repair mechanisms[38]. RAGE engagement activates multiple signaling pathways (Figure 1), including reactive oxygen species, p21ras, erk1/2 (p44/p42) mitogen-activated protein kinases, p38 and SAPK/JNK mitogen-activated protein kinases, rhoGTPases, phosphoinositol-3 kinase and JAK/STAT pathway, with important downstream inflammatory consequences, such as the activation of nuclear factor-kappaB (NFκB), AP-1 and STATs, which are involved in the inflammatory process seen in both diabetes and cancer.

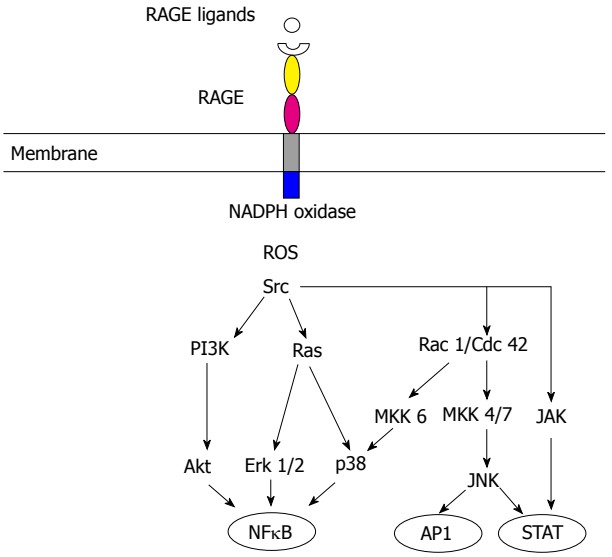

Figure 1 RAGE engagement activates many signaling pathways which are involved in both diabetes-associated vascular complications and tissue damage, and as well as in the tumor microenvironment-associated inflammatory milieu. RAGE: Receptor of advanced glycation end-products.

RAGE, CHRONIC INFLAMMATION AND CANCER

In the nineteenth century, Rudolph Virchow first launched the idea about a putative connection between inflammation and cancer. At present, resurgent research interest in this topic has raised a growing body of evidence supporting the contribution of chronic inflammation to the development of malignancies, as well as an association between the usage of non-steroidal anti-inflammatory agents, and protection against various tumor types[39,40,41,42].

For many years, the relationship between the expression of the receptor of advanced glycation end-products (RAGE) and cancer has been well-documented, as reported in gastric, prostate, lung, pancreas, and liver malignancies. However, the contribution of RAGE to cancer biology seems to be much more functional than initially thought, because it has now emerged as a relevant element that can continuously fuel an inflammatory milieu at the tumor microenvironment[43].

Most of the cancer-promoting effects of RAGE ligands are the result of their interaction with RAGE. Signals downstream of RAGE, drive the strength and maintenance of an inflammatory reaction during tumor promotion in a mouse model of skin cancer, as well as a marked reduction in the number of infiltrating immune cells and the levels of proinflammatory mediators in RAGE$^{-/-}$ animals[44]. In addition, the interaction of the ligands S100A8/A9 with RAGE involve carboxylated glycans; the transition from acute to chronic inflammatory conditions in the study cited did not occur in RAGE$^{-/-}$ mice, which in turn, produced fewer tumors in a colitis-associated cancer model[45].

The consequences of RAGE activation to tumor biology also reach key processes, such as the acquisition of an hypoxia–resistant phenotype in carcinoma cells[46]. Recently, it has been reported that S100A8/A9 proteins contribute to the recruitment and retention of myeloid suppressor cells through a mechanism mediated, at least in part, by the binding to carboxylated N-glycans expressed on the receptor for advanced glycation end-products, and the subsequent activation of the NFκB signaling pathway[47]. AGEs can also down-regulate in vitro the ability of dendritic cells (DCs) to express co-stimulatory signals and to activate T cells[48]. Similar results have been described after a blockade of the autocrine secretion of HMGB1, and of RAGE activation[49,50].

In recent years, a growing body of evidence supports the role of ligands/RAGE axis in angiogenesis. Upon RAGE engagement, profound effects are reported in endothelial cells, including up-regulation of VEGF and metalloproteinase-2, as well as the disruption of the VE-cadherine/catenins complex, thus favoring capillary tube formation[51,52]. Additionally, RAGE activation also increases endothelial permeability to macromolecules, a condition very common in tumor microvasculature[53].

Although many aspects of differentiation, mobilization and recruitment of endothelial progenitor cells (EPCs) remain controversial, it has been reported that the levels of peripheral blood EPCs have been shown to be increased in certain malignant states[54].

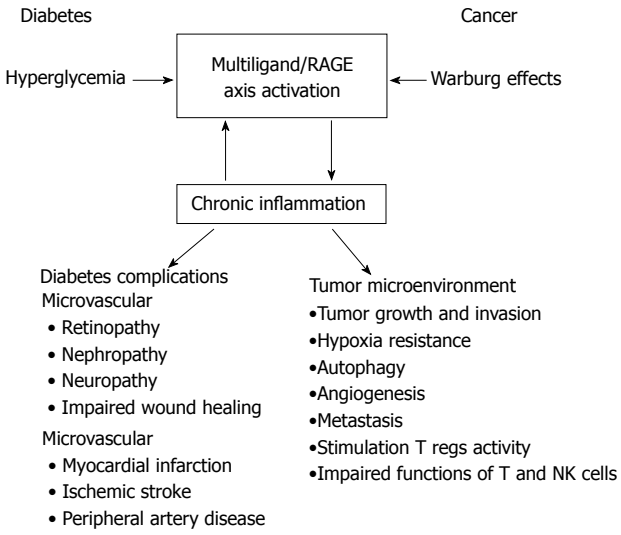

Figure 2 Schematic depiction of consequences of RAGE activation in both diabetes and cancer. A common focal point is the onset and perpetuation of inflammatory conditions.

HMGB1 increased EPCs adhesion to the immobilized integrin ligands intercellular adhesion molecule-1 and fibronectin in a RAGE-dependent manner, thus stimulating EPC homing to ischemic tissues[55].

In 2000, a seminal report on the contribution of multiligand/RAGE axis on invasion and metastasis demonstrated that a blockade of RAGE-HGMB1-derived signaling decreased growth and metastases of both implanted tumors, and tumors developing spontaneously in susceptible mice[56].

CONCLUSION

During the last decade, relevant advances in our understanding of the pathophysiologic role of the multiligand/RAGE axis have lead to a substantial knowledge of how this promiscuous receptor, once activated, is able to continuously bring about an inflammatory milieu (Figure 2). The current relevance of Virchow´s postulate about the role of chronic inflammation in cancer development highlights the facts associated with the presence of an activated RAGE axis, smoldering inflammation such as that occurring in diabetes, and thus its contribution towards the understanding of the mechanistic scenario supporting the link between diabetes and cancer.

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REVIEW

Unravelling the story of protein misfolding in diabetes mellitus

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Abstract

Both environmental and genetic factors contribute to the development of diabetes mellitus and although monogenic disorders are rare, they offer unique insights into the fundamental biology underlying the disease. Mutations of the insulin gene or genes involved in the response to protein misfolding cause early onset diabetes. These have revealed an important role for endoplasmic reticulum stress in β-cell survival. This form of cellular stress occurs when secretory proteins fail to fold efficiently. Of all the professional secretory cells we possess, β-cells are the most sensitive to endoplasmic reticulum stress because of the large fluctuations in protein synthesis they face daily. Studies of endoplasmic reticulum stress signaling therefore offer the potential to identify new drug targets to treat diabetes.

Key words: Endoplasmic reticulum stress; Diabetes; Unfolded protein response; PKR-like ER kinase

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INTRODUCTION

We place a heavy burden on our pancreatic β-cells. They are expected to deliver a life-long supply of insulin at the precise levels necessary to maintain glucose homeostasis while avoiding hypoglycaemia. This requires that they synthesize and secrete insulin at times of plenty, but rapidly attenuate protein synthesis when the hormone is no longer needed. Consequently, the secretory pathway of a β-cell experiences dramatic changes in client protein flux. As a consequence, it is exquisitely sensitive to defects of protein folding because large increases in the rate at which new proteins enter the endoplasmic reticulum (ER) can overwhelm the resident chaperones. This can allow incorrectly folded proteins to accumulate inside the organelle, a situation termed "endoplasmic reticulum stress". Evidence accrued over the last decade has shown that ER stress plays an important role in the pathogenesis of diabetes, both through direct toxicity to the β-cell causing loss of β-cell mass and in peripheral tissues where it contributes to insulin resistance. We propose that current views of diabetes should be revised, so that it is seen as another member of the growing list of protein misfolding diseases.

GENETIC STUDIES IDENTIFYING ER PROTEINS IN THE DEVELOPMENT OF DIABETES MELLITUS

A critical observation was made almost forty years ago when three siblings, two brothers and a sister, were reported who had developed permanent neonatal diabetes mel-

litus in association with developmental bone defects[1]. The parents of those first cases were unrelated, but many subsequent case reports were of consanguineous families[2,3]. The condition now eponymously named Wolcott-Rallison syndrome (OMIM #226980)[4] is also known as multiple epiphiseal dysplasia with early onset diabetes mellitus (MED-IDDM) to highlight its extra-pancreatic manifestations. Indeed, these are diverse and include osteoporosis, growth retardation, hepatic and renal dysfunction and cognitive impairment. It is now known to be inherited as a classical autosomal recessive trait and has been mapped in two consanguineous families to the region 2p12[2]. Each family harbored a distinct mutation, but both proved to be in the *Perk* gene.

PERK is a ubiquitously expressed kinase localized to the membrane of the ER[5,6]. Protein sequence homology showed it to be a member of the eIF2α kinase family that links cellular stresses to the inhibition of protein translation. For example, the prototypical family member GCN2 reduces protein synthesis during periods of amino acid starvation by phosphorylating and thus inhibiting the translation initiation factor eIF2α[7]. Other members of this family inhibit protein synthesis during viral infection (PKR[8]) or iron deficiency in red blood cell progenitors (HRI[9]). In each instance, reduced protein synthesis promotes cellular health, by reducing the consumption of amino acids during starvation or preventing viral replication or matching haemoglobin synthesis to available haeme. In the case of PERK, reduced protein synthesis prevents new proteins entering the ER when they cannot be correctly folded. It transpires that PERK is essential for β-cells to withstand fluctuations in proinsulin synthesis that occur daily. Mice in which the *Perk* gene is deleted faithfully recapitulate many of the phenotypic features of Wolcott-Rallison syndrome and this has been very useful in understanding this condition[10]. Remarkably, these mice are born with normal islets of Langerhans, but rapidly lose β-cells in the neonatal period. Prior to death, these cells exhibit ER dilatation, due to distention with aggregates of misfolded proinsulin.

When circulating glucose levels are low, so is the demand for insulin and PERK is inactive. When proinsulin enters the ER it is bound reversibly by molecular chaperones, such as BiP, to promote its correct folding. In addition, chaperones shield newly synthesized proteins from inappropriate interactions with other incompletely folded proteins. When glucose levels rise, β-cells are stimulated to increase insulin synthesis. If this increase were unregulated, the rise in proinsulin synthesis might overwhelm ER chaperones causing ER stress and threatening to cause protein aggregation. Indeed, this occurs in the β-cells of Wolcott-Rallison patients and in *Perk* knockout mice leading to cell death. However, in healthy cells, PERK detects this rise in ER client protein demand by monitoring the level of free BiP in the ER lumen. When free BiP levels fall due to its binding to newly synthesized protein, this triggers PERK to phosphorylate eIF2α and protein translation levels fall. In parallel, ER stress signaling pathways cause an increase in many ER resident proteins including molecular chaperones, which enable higher levels of client proteins to be folded. This mechanism has been called the Unfolded Protein Response (UPR)[11,12]

The major client protein of the β-cell ER is proinsulin[12]. Recently, defects in insulin folding have been shown to underlie rare cases of familial permanent neonatal diabetes mellitus (OMIM #606176)[13]. Initially discovered in mice by Dr. Akio Koizumi in Akita, Japan, a spontaneous *INS2* gene mutation causes β-cell death[14]. In contrast to man, mice possess two insulin genes that are functionally redundant[15] and yet the Akita mutation (C96Y) behaves as a semi-dominant trait[14,16]. This toxic-gain-of-function is caused by a substitution of a conserved cysteine residue required for the formation of an intra-molecular disulphide bond[17,18]. The mutant insulin fails to be secreted and is instead retained in the ER where, crucially, wildtype proinsulin also becomes trapped in complexes with Akita mutant proinsulin impairing secretion of the normal protein[14,19,20]. When a three-generation family with permanent neonatal diabetes mellitus was found to have a heterozygous mutation of the insulin gene, this led to 83 similar families being screened, nine of which harbored insulin mutations including one analogous to the Akita mutation of mice[13]. Several subsequent studies have also confirmed that missense mutations of the *INS* gene in man are a rare but important cause of neonatal diabetes[21-24]. When such mutant insulins were expressed in cultured cells, they caused ER sress and impaired cell viability[22,25]. This contrasts with mutations that impair proinsulin synthesis through impaired transcription, which are inherited recessive traits and fail to cause death of the β-cell[26].

EMERGING MODEL FOR ENDOPLASMIC RETICULUM STRESS INVOLVEMENT IN DIABETES

The precise details of UPR signaling and its links to cell death have been reviewed elsewhere[11,12,27]. However, it is worth examining some aspects of ER stress and cell death again, as these may provide a novel target for therapeutic intervention in the future. For example, Dr Seiichi Oyadomari observed that deletion of the *Chop* gene could delay the onset of diabetes in Akita mice[28] and prevent β-cell death following other toxic stresses[29]. CHOP is a transcription factor that is up-regulated by a number of cellular insults, notably ER stress. It has been linked to the induction of cell death and some have suggested its function is to kill cells when the degree of ER stress is insurmountable[30-32]. However, our work has suggested that the link to cell death is more complex and most likely stems from CHOP acting to boost the secretory capacity of the cell[33]. We showed that the *Gadd34* gene is transcriptionally induced by CHOP during ER stress and that deleting *Gadd34* was at least as protective as deleting the *Chop* gene in an animal model of ER stress. GADD34 functions to dephosphorylate eIF2α following ER stress so that protein translation can recover and UPR target genes can be transla-

ted[34,35]. In this manner, it behaves as a functional antagonist of PERK. Whilst cells lacking PERK are vulnerable to death during ER stress, it appears that the antagonism of PERK by GADD34 during ER stress can also result in cell death. Excessive activity of GADD34 in some circumstances creates a situation similar to that of PERK deficiency. Could GADD34 inhibitors therefore prove useful to treat diabetes? A molecule called salubrinal has been identified that promotes eIF2α phosphorylation during ER stress[36]. Its precise mechanism of action requires further elucidation, but has been suggested to involve inhibition of eIF2α dephosphorylation, which can promote cell survival in some models of ER stress.

When mice were generated with β-cells that were partially resistant to PERK by mutating the phosphorylation site of eIF2α (eIF2α^{S51A}), the animals developed diabetes due to uncontrolled proinsulin synthesis and increased oxidative stress[37]. Feeding them antioxidants in their diet ameliorated this. Interestingly, CHOP induces the transcription of *ERO1a*, which increases protein oxidation in the ER to promote disulphide bond formation[33].While this may improve protein folding, it also imposes an oxidative stress burden on the β-cell. Consequently, preventing the induction of *ERO1a* may explain why *Chop* knockout reduces oxidative damage and improves β-cell survival in models of diabetes[38]. *Chop* deletion also increases β-cell mass and prevents glucose intolerance both in high-fat fed eIF2α^{S51A} mice and in leptin receptor deficient mice. This appears to be mediated by increased β-cell proliferation and by reduced apoptosis suggesting that CHOP antagonism might help maintain β-cell mass in patients if this could be achieved pharmacologically.

β-cells, therefore, can be subject to ER stress either from poorly regulated proinsulin synthesis in Wolcott-Rallison syndrome or directly from mutant proinsulins. It is less clear, however, why ER stress should be relevant in peripheral tissues in diabetic patients. Nevertheless, ER stress in peripheral tissues plays at least as important a role in diabetes as it does in the β-cell. Some peripheral tissues, for example adipocytes, respond to raised circulating glucose by increasing ER protein synthesis thus increasing ER client load[39]. In addition, obesity increases peripheral tissue inflammation, which can also cause ER stress[40,41]. A consequence of this appears to be impaired insulin signaling and consequently insulin resistance.

While PERK regulates protein translation during ER stress and has further effects on UPR gene transcription, a second ER stress sensor called IRE1 regulates other UPR genes. IRE1 is far older than PERK in evolutionary terms, being found even in yeast. Not only can it trigger gene transcription but it can, at least in mammals, also impair insulin receptor signaling. Activated insulin receptors signal to the cell's interior *via* the phosphorylation of target molecules including insulin receptor substrate 1 (IRS1) on tyrosine residues. This can be blocked if IRS1 is phosphorylated on serine residues by the Jun N-terminal kinase (JNK)[42] and is triggered in peripheral tissues of obese subjects through activation of JNK by IRE1[43]. The notion that peripheral ER stress can impair glucose homeostasis is supported by a number of other lines of evidence. For example, if ER function is impaired in the liver by deleting the chaperone Oxygen-Regulated Protein 150 (ORP150), mice display impaired IRS1-dependent insulin signaling and develop glucose intolerance[44]. In contrast, raising the levels of ORP150 protects obese mice from diabetes[44,45]. We may yet be able to use these observations in therapies, since two small molecular "chemical chaperones", 4-phenyl butyric acid and taurine-conjugated ursodeoxycholic acid, relieve ER stress in animal models *in vivo* and improve peripheral insulin sensitivity in obese diabetic mice[46].

CONCLUSION

Substantial clinical and experimental evidence clearly shows that ER stress is important in diabetes both affecting β-cell survival and contributing to peripheral insulin resistance. This novel paradigm has already shed light on poorly understood aspects of diabetes and is providing exciting new targets for therapeutic intervention. Novel molecules, for example salubrinal and guanabenz, are already becoming available to help study ER stress in the laboratory and these may perhaps represent the lead compounds in the development of new drugs that will enable us to tackle ER stress in diabetes and will eventually help to treat this important cause of human suffering.

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FL, United States

January 28, 2011
Diabetes UK and External Conferences
Diabetes Awareness Training
London, United Kingdom

January 28-29, 2011
9. Gastro Forum München
Munich, Germany

February 13-27, 2011
Gastroenterology: New Zealand CME Cruise Conference
Sydney, NSW, Australia

February 16-19, 2011
The 4th International Conference on Advance Technologies & Treatments for Diabetes
London, United Kingdom

February 24-26, 2011
2nd International Congress on Abdominal Obesity
Buenos Aires, Brazil

February 26-March 1, 2011
Canadian Digestive Diseases Week, Westin Bayshore, Vancouver
British Columbia, Canada

February 28-March 1, 2011
Childhood & Adolescent Obesity: A Whole-system Strategic Approach
Abu Dhabi, United Arab Emirates

March 3-5, 2011
42nd Annual Topics in Internal Medicine
Gainesville, FL, United States

March 14-17, 2011
British Society of Gastroenterology Annual Meeting 2011, Birmingham
England, United Kingdom

March 17-20, 2011
Mayo Clinic Gastroenterology & Hepatology
Jacksonville, FL , United States

March 18, 2011
UC Davis Health Informatics: Change Management and Health Informatics, The Keys to Health Reform
Sacramento, CA, United States

March 25-27, 2011
MedicReS IC 2011 Good Medical Research
Istanbul, Turkey

March 28–30, 2011
The Second World Congress on Interventional Therapies for Type 2 Diabetes
New York, United States

April 25-27, 2011
The Second International Conference of the Saudi Society of Pediatric Gastroenterology, Hepatology & Nutrition
Riyadh, Saudi Arabia

May 7-10, 2011
Digestive Disease Week
Chicago, IL, United States

June 2-5, 2011
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Shanghai, China

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October 22-26, 2011
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INSTRUCTIONS TO AUTHORS

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 200201 03498. 2002 Aug 1

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