A Brief Overview about MAPK14 Gene Association with Diabetic Foot Ulcers

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Abstract

Diabetic foot ulcer (DFU) is a leading cause of morbidity and mortality associated with significant healthcare costs. Along with a life-time risk of up to 25%, DFUs account for approximately 25% of all hospital stays for patients with diabetes and about two-thirds of all nontraumatic amputations performed. Epidemiological studies have suggested multiple risk factors for DFUs: diabetic neuropathy, peripheral vascular disease, biomechanical factors, previous foot ulceration, poor glycaemic control, longer duration of diabetes, smoking, ethnicity, retinopathy, nephropathy, insulin use, poor vision, age and male sex. MAPK14 encodes p38α mitogen-activated protein kinase (MAPK) which is the prototypic member of the p38 MAPK family. p38 MAPKs are also known as stress-activated serine/threonine-specific kinases (SAPKs). In addition to MAPK14 for p38α MAPK, the p38 MAPK family has three additional members, including MAPK11, MAPK12 and MAPK13 which encodes p38β MAPK, p38γ MAPK and p38δ MAPK isoforms, respectively. p38α MAPK was originally identified as a tyrosine phosphorylated protein detected in activated immune cell macrophages with an essential role in inflammatory cytokine induction, such as Tumor Necrotic Factor α (TNFα). 6 Thereby, the MAPK14 protein is also implicated to affect wound healing, while its specific function appears to depend on cell type as well as exogenous and endogenous stimuli.

Keywords: MAPK14, diabetic foot ulcers

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Introduction

Diabetes mellitus (DM) is probably one of the oldest diseases known to man. It was first reported in Egyptian manuscript about 3000 years ago.[1] In 1936, the distinction between type 1 and type 2 DM was clearly made.[2] Type 2 DM was first described as a component of metabolic syndrome in 1988.[3] Type 2 DM (formerly known as non-insulin dependent DM) is the most common form of DM characterized by hyperglycemia, insulin resistance, and relative insulin deficiency.[4] Type 2 DM results from interaction between genetic, environmental and behavioral risk factors.[5,6]

People living with type 2 DM are more vulnerable to various forms of both short- and long-term complications, which often lead to their premature death. This tendency of increased morbidity and mortality is seen in patients with type 2 DM because of the commonness of this type of DM, its insidious onset and late recognition, especially in resource-poor developing countries like Africa.[7]

Epidemiology

It is estimated that 366 million people had DM in 2011; by 2030 this would have risen to 552 million.[8] The number of people with type 2 DM is increasing in every country with 80% of people with DM living in low- and middle-income countries. DM caused 4.6 million deaths in 2011.[8] It is estimated that 439 million people would have type 2 DM by the year 2030.[9] The incidence of type 2 DM varies substantially from one geographical region to the other as a result of environmental and lifestyle risk factors.[10]

Literature search has shown that there are few data available on the prevalence of type 2 DM in Africa as a whole. Studies examining data trends within Africa point to evidence of a dramatic increase in prevalence in both rural and urban setting, and affecting both gender equally.[11]

The majority of the DM burden in Africa appears to be type 2 DM, with less than 10% of DM cases being type 1 DM.[11] A 2011 Centre for Disease Control and Prevention (CDC) report estimates that DM affects about 25.8 million people in the US (7.8% of the population) in 2010 with 90% to 95% of them being type 2 DM.[12]

It is predicted that the prevalence of DM in adults of which type 2 DM is becoming prominent will increase in the next two decades and much of the increase will occur in developing countries where the majority of patients are aged between 45 and 64 years.[13] It is projected that the latter will equal or even exceed the former in developing nations, thus culminating in a double burden as a result of the current trend of transition from communicable to non-communicable diseases.[14]

Diabetic foot ulcers (DFU) are common clinical problems and devastating complications of diabetes, and affect 15% of all diabetic patients and results in significant morbidity, mortality, and financial burdens[1]. Five-year risk of mortality for a patient with diabetic foot ulcer is 2.5 times higher than the risk for a patient without[2]. Approximately 20% of moderate or severe DFU could cause some level of amputation. Moreover, 74% of them also have a risk of renal replacement therapy at 2 years[3]. This high mortality rate is also related with coexisting comorbidities such as cardiovascular or cerebro-vascular diseases.

The pathophysiology of DFU is based on a triad of neuropathy, peripheral arterial disease, and concomitant secondary bacterial infection. Peripheral neuropathy could lead to intrinsic muscle atrophy and functional anatomical changes in the foot[4]. Eventually, progressive secondary foot infection penetrating deep facia, tendons, and joints could develop with repetitive inattention trauma. Infection could play a significant role for half of major lower limb extremity amputations. Recent studies indicate some risk factors for the development of DFU. These are as follows: Longer than 10 years of duration of diabetes, male gender, older patients, presence of comorbidities including nephropathy, neuropathy, and peripheral vascular disease, and history of foot ulceration[4-6].

The management of DFU is usually complex and challenging to clinicians in clinical practice. Costs of diabetic foot ulcerations have been increased to the treatment cost of many common cancers. Estimated costs of DFU management are greater than 1 billion in both developed and developing countries. Therefore, foot ulcers should be treated immediately by a multidisciplinary expert team for optimal outcomes. The treatment of DFU requires an immediate decision and systematic approach that comprises of maintaining arterial blood flow, treating the infection appropriately, and removing the pressure from the wound[7]. In addition, several adjuvant therapies are becoming a popular form of diabetic foot treatment. During the past 10 years, there has been an increasing amount of novel, basic science-based approaches and developments for adjuvant therapies including wound dressing, hyperbaric oxygen therapy, or growth factor formulations for efficient local delivery[8-10].

MAPK14 encodes p38α mitogen-activated protein kinase (MAPK) which is the prototypic member of the p38 MAPK family. p38 MAPKs are also known as stress-activated serine/threonine-specific kinases (SAPKs). In addition to MAPK14 for p38α MAPK, the p38 MAPK family has three additional members, including MAPK11, MAPK12 and MAPK13 which encodes p38β MAPK, p38γ MAPK and p38δ MAPK isoforms,

respectively. p38α MAPK was originally identified as a tyrosine phosphorylated protein detected in activated immune cell macrophages with an essential role in inflammatory cytokine induction, such as Tumor Necrotic Factor α (TNFα).[6][7] However, p38α MAPK mediated kinase activity has been implicated in many tissues beyond immune systems. p38α MAPK is mainly activated through MAPK kinase kinase cascades and exerts its biological function via downstream substrate phosphorylation. p38α MAPK is implicated in diverse cellular functions, from gene expression to programmed cell death through a network of signaling molecules and transcription factors. Pharmacological and genetic inhibition of p38α MAPK not only revealed its biological significance in physiological function but also the potential of targeting p38α MAPK in human disease such as immune disorders and heart failure.

Structure

MAPK14 is a 41 kDa protein composed of 360 amino acids.[8][9]

Function[edit]

The protein encoded by this gene is a member of the MAP kinase family. MAP kinases act as an integration point for multiple biochemical signals, and are involved in a wide variety of cellular processes such as proliferation, differentiation, transcription regulation and development. This kinase is activated by various environmental stresses and proinflammatory cytokines. The activation requires its phosphorylation by MAP kinase kinases (MKKs), or its autophosphorylation triggered by the interaction of MAP3K7IP1/TAB1 protein with this kinase. The substrates of this kinase include transcription regulator ATF2, MEF2C, and MAX, cell cycle regulator CDC25B, and tumor suppressor p53, which suggest the roles of this kinase in stress-related transcription and cell cycle regulation, as well as in genotoxic stress response. Four alternatively spliced transcript variants of this gene encoding distinct isoforms have been reported.[10]

p38α MAPK is ubiquitously expressed in many cell types, in contrast, p38β MAPK is highly expressed in brain and lung, p38γ MAPK mostly in skeletal muscle and nerve system, and p38δ MAPK in uterus and pancreas.[11][12] Like all MAP kinases, p38α MAPK has 11 conserved domains (Domains I to XI) and a Thr-Gly-Tyr (TGY) dual phosphorylation motif. Activation of p38 MAPK pathway has been implicated in a variety of stress response in addition to inflammation, including osmotic shock, heat, and oxidative stress.[11][13][14] The canonical pathway for p38 MAPK activation involve a cascade of protein kinases, including MAP3K such as MEKK1, 2, 3 and 4, TGFβ-activated kinase (TAK1), TAO1-3, mixed-lineage kinase 2/3 (MLK2/3), and apoptosis signal-regulating kinase 1/2 (ASK1/2), as well as MAP2Ks, such as MKK3, 6 and 4. MAP2K mediated phosphorylation of the TGY motif results in conformational change of p38 MAPK which allows kinase activation and accessibility to substrates.[15] In addition, TAK1-binding protein 1 (TAB1) and ZAP70 can induce p38 MAPK via non-canonical autophosphorylation.[16][17][18] Furthermore, acetylation of p38 MAPK at lys-53 of the ATP-binding pocket also enhances p38 MAPK activity during cellular stress[19] Under basal conditions, p38α MAPK is detected in both the nucleus and the cytoplasm. One of the consequences of p38 MAPK activation is translocation into the nucleus.[20] involving both p38 MAPK phosphorylation and microtubule- and dynein-dependent process.[21] In addition, one substrate of p38 MAPK, MAP kinase-activated protein kinase 2 (MAPAK2 or MK2) can modulate and direct p38α MAPK localization to cytosole via direct interaction.[22] p38α MAPK activation can be reversed by dephosphorylation of the TGY motif carried out by protein phosphatases, including ser-thr protein phosphatases (PPs), protein tyrosine phosphatases (PTP), and dual-specificity phosphatases (DUSP). For example, ser/thr phosphatases PP2Cα/β suppress activity of p38s MAPK through direct interaction as well as suppression of MKKs/TAK1 in mammalian cells.[23][24] Hematopoietic PTP (HePTP) and striatal-enriched phosphatase (STEP) bind to MAPKs through a kinase-interaction motif (KIM) and inactivates them by dephosphorylating the phosphotyrosine residue in their activation loop.[25][26][27] DUSPs, which have a docking domain to MAPKs and dual-specific phosphatase activity, can also bind to p38 MAPKs and dephosphorylate of both phosphotyrosine and phosphothreonine residues.[15] In addition to these phosphatases, other molecular components such as Hsp90-Cdc37 chaperone complex can also modulate p38 MAPK autophosphorylation activity and prevents non-canonical activation.[28]

p38α MAPK is implicated in cell survival/apoptosis, proliferation, differentiation, migration, mRNA stability, and inflammatory response in different cell types through variety of different target molecules[29] MK2 is one of the well-studied downstream targets of p38α MAPK. Their downstream substrates include small heat shock protein 27 (HSP27), lymphocyte-specific protein1 (LSP1), cAMP response element-binding protein (CREB), cyclooxygenase 2 (COX2), activating transcription factor 1 (ATF1), serum response factor (SRF), and mRNA-binding protein tristetraprolin (TTP)[20][30] In addition to protein kinases, many transcription factors are downstream targets of p38α MAPK, including ATF1/2/6, c-Myc, c-FOS, GATA4, MEF2A/C, SRF, STAT1, and CHOP[31][32][33][34]

Role in cardiovascular system[edit]

p38α MAPK constitutes the main p38 MAPK activity in heart. During cardiomyocyte maturation in new born mouse heart, p38α MAPK activity can regulate myocyte cytokinesis and promote cell cycle exit.[35] while inhibition of p38 MAPK activity leads to induction of mitosis in both adult and fetal cardiomyocyte.[36][37] Therefore, p38 MAPK is associated with cell-cycle arrest in mammalian cardiomyocytes and its inhibition may represent a strategy to promote cardiac regeneration in response to injury. In addition, p38α MAPK induction promotes myocyte apoptosis.[38][39] via downstream targets STAT1, CHOP, FAK, SMAD, cytochrome c, NF-κB, PTEN, and p53.[40][41][42][43][44][45][46] p38 MAPK can also target IRS-1 mediated AKT signaling and promotes myocyte death under chronic insulin stimulation.[47] Inhibition of p38 MAPK activity confers cardioprotection against ischemia reperfusion injury in heart[48][49] However, some reports demonstrated that p38 MAPK also involves in anti-apoptotic effect via phosphorylation of αβ-Crystallin or induction of Pim-3 during early response to oxidative stress or anoxic preconditioning respectively[50][51][52] Both p38α MAPK and p38β MAPK appear to have an opposite role in apoptosis.[53] Whereas p38α MAPK has a pro-apoptotic role via p53 activation, p38β MAPK has a pro-survival role via inhibition of ROS formation.[54][55] In general, chronic activation of p38 MAPK activity is viewed as pathological and pro-apoptotic, and inhibition of p38 MAPK activity is in clinical evaluation as a potential therapy to mitigate acute injury in ischemic heart failure.[56] p38 MAPK activity is also implicated in cardiac hypertrophy which is a significant feature of pathological remodeling in the diseased hearts and a major risk factor for heart failure and advert outcome. Most in vitro evidence supports that p38 MAPK activation promotes cardiomyocyte hypertrophy.[53][57][58][59] However, in vivo evidence suggest that chronic activation of p38 MAPK activity triggers restrictive cardiomyopathy with limited hypertrophy,[60] while genetic inactivation p38α MAPK in mouse heart results in an elevated cardiac hypertrophy in response to pressure overload[61][62] or swimming exercise.[63] Therefore, the functional role of p38 MAPK in cardiac hypertrophy remains controversial and yet to be further elucidated. .[64-65]

In Scotland, patients with diabetes are invited to attend an annual free foot screening and to have their feet checked by podiatrists.[65]The screening aims to identify diabetic foot complications at an early stage to prevent or delay serious consequences such as lower-limb amputation. During the screening, podiatrists not only record the clinical conditions of foot ulcers, if any (including area, size and depth), but also clinical characteristics that might be linked with DFUs, such as the presence or absence of foot pulses, nerve sensation and vibration functions, previous ulceration history, significant structural foot deformity, presence of callus, amputation history and self-care ability. However, in the current version (June 2014) of e-health records provided by SCI-DC to researchers, the detailed descriptions of ulcers such as area, size and depth are not available. DFUs are categorized as current ulcers (left leg and right leg) and previous ulcers (left leg and right leg) in a longitudinal manner based on examination dates.

Asuthors have identified the SNP rs80028505, which achieved GWAS significance ($P = 2{\cdot}45 \times 10^{-8}$, odds ratio 1·71). This SNP was supported by a cluster of nearby SNPs that also showed significant GWAS *P*-values. The SNP cluster was in *MAPK14*, which is a protein-coding gene located on chromosome 6. This gene is widely expressed in multiple organs, including skin and soft tissues. [66]The mitogen-activated protein kinase (MAPK)14 protein, an enzyme also called p38-α, is one of the four p38 MAPKs that play an essential role in the cascade of cellular responses evoked by extracellular stimuli such as proinflammatory cytokines or physical stress leading to direct activation of transcription factors. [67] Evidence from a diabetic mouse model has suggested that p38 MAPK was phosphorylated in wounded skin and using a p38 MAPK

inhibitor, the level of phosphorylation was significantly reduced and wound healing was accelerated. This was evidenced by reduced wound width, accelerated re-epithelialization, increased granulation and reduced inflammatory cell infiltration into the wound. [68]

However, the effect of the MAPK pathway on wound healing is controversial in some studies. For example, activation of the MAPK pathway has been suggested to promote cell collective migration, a biological process involved in tissue formation and repair. [69] By applying a MAPK inhibitor to a diabetic rat wound model, the rate of wound healing was reported to be reduced by 20%.[70]It was also reported that MAPK inhibitors can reverse cutaneous wound-healing effects in a nondiabetic mouse wounding model. [71]In fact, both acute and chronic wound healing abilities are impaired in diabetes and the MAPK pathway has been confirmed to be activated. [72-75] The MAPK pathway is also involved in other types of ulcers, such as venous ulcer, gastric ulcer and corneal ulcer. [75-78] Most SNPs in *MAPK14* affect *MAPK14* expression ($P = 10^{-7}$) according to the Genotype-Tissue Expression (GTEx, Broad Institute of MIT and Harvard, Cambridge, MA, U.S.A.) portal, particularly in skin. [79-83]

SO, it is proposed that MAPK14 could associated with DFUs with diabetes using a GWAS approach. However There are very few studies to demonstrate the possible association between MAPK14 gene and diabetic foot ulcer, Future studies are needed to identify genetic contributors to the development of DFUs in the presence of peripheral neuropathy.

No Conflict of interest.

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