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High Pressure as a Mechanical Stress and Mitogen-Activated Protein Kinase Activation in Glomerular Diseases

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Abstract Progressive renal diseases lead to prolonged glomerular hypertension, which acts as a mechanical stress to mesangial cells and induces the proliferation of mesangial cells. In mesangial cell proliferation, various growth factors and mitogenic stimuli are known to induce the activation of mitogen-activated protein kinase (MAPK), which serves as an important regulator of transcriptional activity with cell proliferation. Here I review the relationship of glomerular hypertension as a mechanical stress and MAPK activation, which induces glomerular sclerosis through proliferation in mesangial cells.

Key Words: mechanical stress, MAP kinase, mesangial cell

Introduction

Mechanisms of the progression of chronic renl failure are at present largely unknown. Glomerular capillary hypertension could be a major factor in the development of chronic renal failure[1,2]. Progressive renal diseases such as diabetic nephropathy, remnant kidney, and glomerular sclerosis lead to glomerular hypertension, which is thought to bring about further renal injuries. However, the effects of this hemodynamic abnormalities on glomerular cells and detailed mechanisms are unknown. In this paper, the effect of glomerular hypertension as a mechanical stress on mesangial cells and its signal transduction mechanisms are reviewed.

Effect of hypertension as a mechanical stress on glomerular cells

Mesangial cells in glomeruli are located under a fenestrated capillary endothelium, and are exposed to hydrostatic pressure necessary to sustain normal filtration[3,4]. Progressive renal diseases such as diabetic nephropathy, remnant kidney, and hypertensive nephropathy, lead to prolonged glomerular hypertension, which is involved in the mesangial cell proliferation that is considered to be the most important factor mediating glomerular sclerosis[1,5,6]. Glomerular pressure directly pressurizes mesangial cells through a fenestrated endothelium, because mesangial cells and glomerular capillaries are surrounded by mesangial matrices and a continuous basement membrane composed of several types of collagens. This force affects mesangial cells as a mechanical stress, which induces various gene expression and cellular response[7-9]. Besides, glomerular pressure is thought to induce stretch of mesangial cells[3], which causes mechanical strain to mesangial cells. Mechanisms of these changes under glomerular hypertension remain largely unknown, although stretch of cultured mesangial cells stimulates proliferation and synthesis of extracellular matrix[10,11].

In recent studies, using a pressure loading apparatus, high pressure allowing for several levels of air pressure was applied to mesangial cells, to examine the effects of hydrostatic pressure on the proliferation of cultured rat mesangial cells[7-9]. These studies indicated that pressure by itself increases DNA synthesis and proliferation of cultured rat mesangial cells. These results show that high pressure induces proliferation of mesangial cells through cell cycle progression.

Cell cycle control and mitogen-activated protein kinase

Various growth factors and mitogenic stimuli are known to induce the activation of mitogen-activated protein kinase (MAPK) , a serine/threonine kinase[12,13]. This kinase activity is up-regulated through phosphorylation on tyrosine and threonine residues by MAPK/extracellular signal-regulated kinase kinases (MEKs) [14,15]. MEKs are substrates for Raf-1[16,17], which has been reported to be activated either through receptors involved in Ras or a PKC-dependent pathway[18,19]. These MAPK activators cause the translocation of MAPK from the cytosol to the nucleus[20-22] where transcription factors such as Elk-1[23] and c-Ets[24,25] are substrates for MAPK. This indicates that MAPK serves as an important regulator of transcriptional activity related to proliferation. Recent studies show that both G1/S and G2/M transitions, which are important cell cycle-related events for proliferation , are regulated positively by MAPK[26,29]. Therefore, increasing attention has been paid to the role of MAPK in the cell cycle.

Effect of high pressure as a mechanical stress on MAPK

The mechanism responsible for the proliferation of mesangial cells under high pressure condition is at present largely unknown. Kawata etal for the first time showed MAPK activation of cells in response to high pressure and consequent activation of cell cycle regulator with cell proliferation[8]. The upstream cascade of MAPK activation is still unknown, although they demonstrated that this kinase activation is involved in tyrosine kinase activation[8].

MAPK is strongly activated by growth factors and growth-promoting hormones[12,17,30-33], in contrast to JNK, which is preferentially activated by environmental stresses and pro-inflammatory cytokines[13,34-36]. In recent studies, applied pressure, which is a physical force generated by hydrostatic pressure, promotes the activation of MAPK but not JNK1[8]. MAPK has been reported to phosphorylate Elk-1, a nuclear transcription factor[37,38]. Elk-1 binds to a serum response element within the c-fos promoter region together with a serum response factor, inducing c-Fos expression[39,41]. High pressure induces c-Fos expression, and the induction is inhibited by both MAPK antisense oligonucleotide and MEK inhibitor[8]. These observations demonstrate that MAPK activation is involved in the expression of c-Fos under high pressure conditions. A transcription factor, c-Ets, is also a substrate for MAPK[42-43]. The promoter region of cyclin D 1 , which plays an important role in the entry of cells into S phase and cell cycle progression[44-47], has an Ets-like binding domain that regulates cyclin D1 expression[24,42]. Recently, Lavoie et al reported that MAPK plays a positive regulatory role in cyclin D1 expression[26]. Consistent with their report, Kawata et al showed that pressure-load activates MAPK, which increases cyclin D1 expression and an enhancement of DNA synthesis and cell growth[8]. Therefore, cyclin D1 expression may participate in pressure-induced proliferation since pressure-load contributes to cell cycling by enhancing G1/S progression and promoting the rate of DNA synthesis in mesangial cells as described previously[7].

Mechanisms of MAPK activation

The mechanism of MAPK activation under high pressure conditions is poorly elucidated. It dose not appear that mesangial cells secrete growth factors that would activate MAPK during pressure-load. MAPK is rapidly activated reaching a peak at 1 min after pressure-load:there seems to be no time delay due to the secretion of growth factors after pressure-load[8]. In addition, applied pressure

induces tyrosine phosphorylation of proteins with molecular weight of 180 kDa, 53 kDa,and 35 kDa, and these tyrosine phosphorylations are inhibited by genistein[8]. Thus, it is strongly suggested that tyrosine kinases are involved in the pressure-induced MAPK activation. Kato et al indicated that pressure increases DNA synthesis and proliferation through activation of protein kinase C and tyrosine kinases, and PDGF-B could be partially involved in these pathways[9]. Some pathways might be involved in the proliferation induced by pressure, since PDGF is expressed at several hours after pressure-loading while MAPK is activated at several minutes. Predicted cascades of pressure-induced proliferation of cultured mesangial cells are shown in Figure.

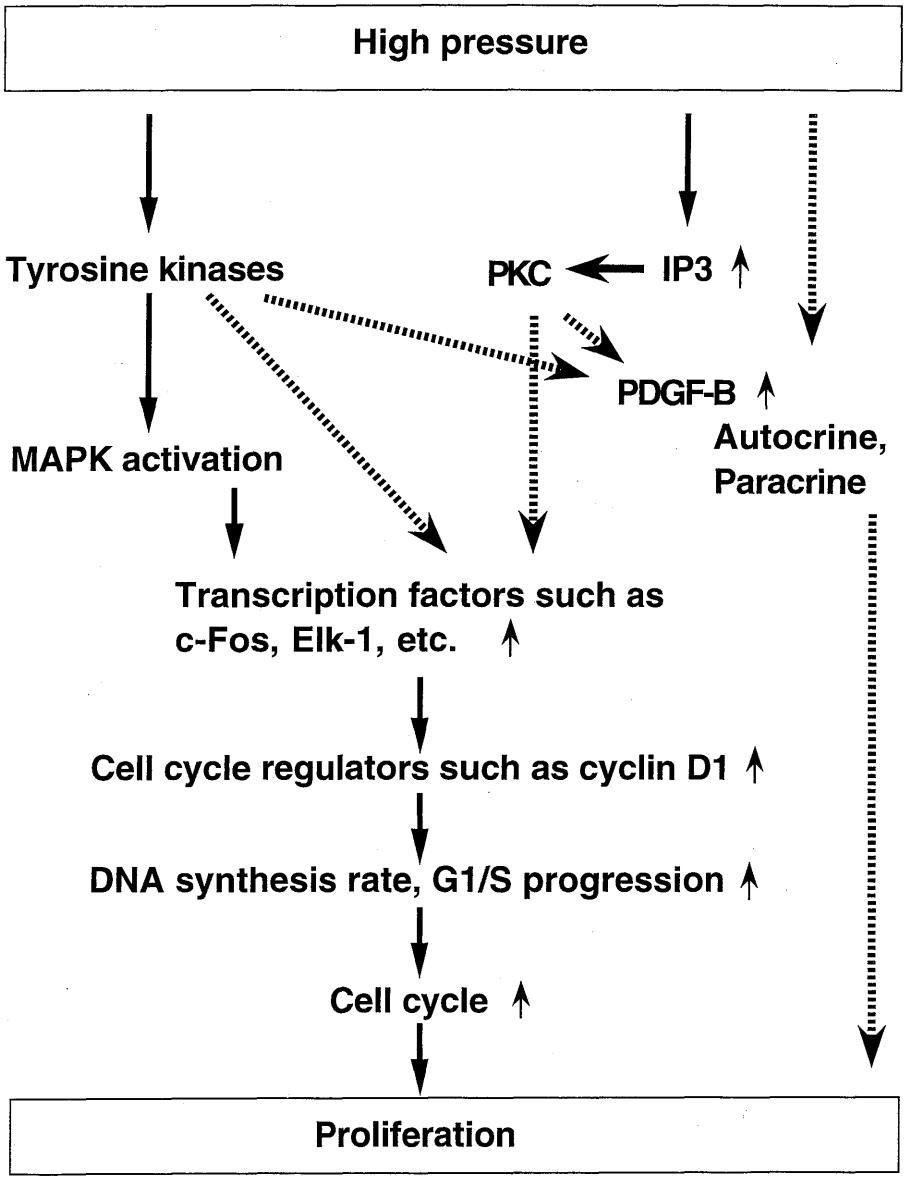

Fig. A scheme of predicted signal transduction cascades of pressure-induced proliferation of mesangial cells. Dotted lines indicate the cascade which has not yet been confirmed.

MAPK activation and renal diseases

MAPK activation in mesangial cells is thought to play an important role in the development of renal injury. Bokemeyer et al have recently reported that MAPK is significantly activated by proliferative glomerulonephritis in response to immune injury [48]. The proliferation induced by renal diseases an important aspect of the pathogenic process of glomerular sclerosis[48]. In the diseases, this is often accompanied not only by the proliferation of mesangial cells but also by expansion of the extracellular matrix[49-51]. Transforming growth factor β (TGFβ) is reported to be a factor in regulating the extracellular matrix and inducing glomerular sclerosis[51,52]. It is known that the promoter region of TGFβ contains an AP1 element[53-56], and that c-Fos expression regulates TGFβ expression. In our studies pressure-load significantly increases the expression of TGFβ in mesangial cells for 24 hr[57]. Pressure-load may increase TGFβ expression through c-Fos induced by MAPK activation. It is possible that pressure-load contributes to the development of renal injury by both mesangial proliferation and matrix expansion through MAPK activation. This MAPK activation of mesangial cells in response to pressure-load might be an underlying mechanism in the development of renal injury with glomerular hypertension. Recent studies demonstrate that mechanical stretch activates MAPK activity, which mediates overproducton of extracellular matrix in mesangial cells[58,59]. These findings suggest that MAPK plays a significant role in glomerular hypertension and glomerular sclerosis.

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