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Potential Roles of TGF-β1 and EMILIN1 in Essential Hypertension

Masanori Shimodaira[1,2] and Tomohiro Nakayama[2,3]
[1]*Department of Internal Medicine, Tokyo Metropolitan Hiroo Hospital, Tokyo,*
[2]*Division of Laboratory Medicine, Department of Pathology and Microbiology, Nihon University School of Medicine, Tokyo,*
[3]*Divisions of Nephrology and Endocrinology, Department of Medicine, Nihon University School of Medicine, Tokyo, Japan*

1. Introduction

Essential hypertension (EH), which in general increases the arterial blood pressure, is a major health concern and risk factor for other diseases such as myocardial infarction and kidney failure (Barri, 2006; Stokes et al., 1989; Mosterd et al., 1999). EH development is known to be multifactorial, with both genetic determinants, such as allelic variation in the genes that are involved in renal salt absorption, and environmental factors that involve the diet (Lifton et al., 2001). The two widely recognized hallmarks of EH are resistance artery narrowing and large artery stiffening, which increase peripheral resistance and compromise vascular compliance, respectively. Both are known to contribute to the progression and cardiovascular morbidity and mortality associated with EH. However, despite decades of study, the initial causes that lead to these vascular abnormalities have yet to be completely elucidated. Moreover, the question remains as to whether these abnormalities exist prior to, and thus participate in, the initial phase of blood pressure elevation, or are a consequence of it.

The extracellular matrix (ECM) in the vascular wall has been found to be a critical determinant, and therefore it is thought that EH is associated with both an increased cardiovascular deposition and an increased systemic turnover of ECM proteins (Diez et al., 1995). Thus, vessel compliance dictated by the ECM is also involved in modulating the blood pressure.

Transforming growth factor (TGF)-β1 is an extracellular polypeptide member of the TGF-β superfamily of cytokines. It is a secreted protein that performs many cellular functions including control of cell growth, cell proliferation, cell differentiation and apoptosis. TGF-β1 acts bifunctionally to elevate blood pressure by first altering levels of vasoactive mediators and then by changing the vessel wall architecture to increase the peripheral resistance. In the cardiovascular system, TGF-β1 may play a key role in the regulation of the mechanical strain-induced matrix synthesis by the human vascular smooth muscle (VSM) cells. If so, this suggests that TGF-β1 may also play an important role in the development of hypertension-induced cardiovascular fibrosis (O'Callaghan&Williams, 2000).

Elastin microfibril interface-located protein 1 (EMILIN1) is a glycoprotein expressed in the vascular tree that binds to the TGF-β1 precursor and prevents processing by furin. Emilin 1 knockout mice display increased TGF-β1 signaling in their vessel walls. These animals develop peripheral vasoconstriction and arterial hypertension, which can be prevented by inactivation of one TGFB1 allele (Zacchigna, et al., 2006). These matrix-dependent changes in the vascular hemodynamics caused by TGF-β1 and EMILIN1 are important because they ultimately affect the cardiovascular morbidity and mortality rates.

This brief review focuses on the important roles of TGF-β1 and EMILIN1 in human hypertension, and in addition, evaluates the available data within the context of the current knowledge that has been collected from animal models of this disease.

2. Transforming growth factor-β1

2.1 The family of TGFs

The family of transforming growth factor (TGF) β belongs to a superfamily that consists of over 25 diverse dimeric extracellular polypeptides of 110-140 amino acids. These polypeptides include bone morphogenetic proteins, activins, and inhibitors (Massague et al., 1994). After discovery of the initial member of the TGF family in 1980 (Roberts et al., 1980), these important molecules have subsequently been shown to have complex effects on organ development, cell growth and differentiation. However, they are particularly important with regard to the expression of ECM proteins. There are three cytokine isoforms of TGF-β in mammals, TGF-β1, TGF-β2, and TGF-β3. All of these isoforms bind to the same receptors. In addition, they are encoded by separate genes sharing 60-80% homology and thus are most likely derived from a common ancestor. The major difference between the isoforms appears to be the spatiotemporal control of their expression patterns. While in vitro TGF-β isoforms have a similar effect on biologic tissues, they are generally characterized in vivo by varied degrees of expression and different functions. Their biologic activity depends on quantitative relationships between the individual isoforms (Cho et al., 2004; Li et al., 1999; Nakamura et al., 2004).

2.2 TGF-β1 in human hypertension

TGF-β1 is recognized as the most pivotal TGF-β isoform for the cardiovascular system, as it is present in VSM cells, endothelial cells, myofibroblasts, macrophages, and other hematopoietic cells (Annes et al., 2003). TGF-β1 strongly up-regulates the production of ECM proteins including fibronectin and collagen (Ignotz&Massague, 1986), and inhibits the degradation of the ECM by tissue proteinases (Laiho&Keski-Oja, 1989). Although TGF-β1 acts in wound healing via its effects on the ECM, excessive TGF-β can cause several fibrotic diseases including glomerulonephritis and diabetic nephropathy (Okuda et al., 1990). While TGF-β1 has long been thought to have only paracrine and autocrine effects, it has now been shown to have wide-ranging systemic (endocrine) effects (Sporn, 1997).

Lin et al. examined the association between serum TGF-β1 levels and gender, age, and selected lifestyle factors in a large number of healthy Japanese control subjects (Lin et al., 2009). They found that serum TGF-β1 levels appear to be modulated in part by gender, age and lifestyle factors such as obesity, cigarette smoking, and alcohol drinking (Lin et al., 2009). Overproduction of TGF-β1 clearly underlies the tissue fibrosis noted in numerous

experimental and human diseases, including EH. Li et al. demonstrated for the first time that a positive correlation exists between circulating TGF-β1 levels and blood pressure in humans (Li et al., 1999). In another previous study, they also reported that the TGF-β1 protein concentration in hypertensive subjects (n=61) was 261±9 ng/ml as compared to 188±7 ng/ml in normotensive controls (n=90) (P<0.0001) (Suthanthiran et al., 2000). Obesity is an independent risk factor for EH and cardiovascular diseases. A strong relationship exists between the body mass index and blood pressure. Porreca et al. have reported that TGF-β1 levels are independently associated with obesity in hypertensive patients (Porreca et al., 2002). In addition, TGF-β1 is positively correlated with the body mass index and creatinine clearance in EH patients (Torun et al., 2007). In adipose tissue from both obese mice and humans, the levels of tissue TGF-β1 antigen have been shown to be well correlated with BMI (Alessi et al., 2000). Moreover, the *TGF-β1* gene was reported to be associated with obesity phenotypes such as BMI, fat mass, and lean mass in a large Caucasian population sample (Long et al., 2003). Likewise, an association was also observed between the TGF-β1 polymorphism and both the BMI and abdominal obesity in Swedish men (Rosmond et al., 2003). These data suggest that elevated levels are not just simply a marker of a similar disease production mechanism, but in fact indicate that elevated levels of circulating TGF-β1 lead to disease production and to the synergy of risk factors that are seen during EH production.

2.3 The synthesis of TGF-β1

TGF-β1 is synthesized by many cell types, including the endothelium, and is secreted as a latent dimeric ~75-kDa protein complex. While the enzyme furin cleaves a latency-associated peptide from the active TGF-β molecule during intracellular processing, it remains noncovalently complexed to the mature peptide after secretion. In addition, latent TGF-β-binding proteins, which are members of the fibrillin/latent TGF-β-binding protein family, bind to this complex and then direct it to the adjacent interstitium. Once in the extracellular space, removal of the latent TGF-β frees the mature, ~24-kDa biologically active form of TGF-β (Annes et al., 2003). Thus, endothelium-derived TGF-β1 is typically a locally acting molecule that has autocrine and paracrine actions on the neighboring endothelium and VSM. There are several known mechanisms of activation for TGF-β1. Thrombospondin-1 is secreted by the endothelial cells and appears to be the major regulatory factor involved in this activation (Schultz-Cherry et al., 1994). However, other factors have been identified that stimulate TGF-β1. For example, increased vascular wall stress that occurs in hypertensive individuals can sufficiently promote a strain "dose-dependent" increase in the TGF-β1 production by VSM cells, which leads to an associated increase in the matrix accumulation (O'Callaghan&Williams, 2000). Norepinephrine (Briest et al., 2004), hypoxia (Lee et al., 2009), oxidative stress (Zhao et al., 2008) and high glucose levels (Iglesias-de la Cruz et al., 2002) have also been shown to induce TGF-β1 production. Most of the information known about TGF-β1 has been collected from in vitro and in vivo animal models. Since human TGF-β1 and its nonhuman counterparts share a sufficiently high degree of homology, this makes it possible to extrapolate relevant data from animals to humans.

The Smad proteins (Smad2, Smad3 and Smad7) are essential components of the downstream TGF-β signaling. Positive signaling via activation of Smad2/3, along with negative signaling

via the negative feedback mechanism of Smad7, are able to regulate the biological activities of TGF-β1 (Kretzschmar&Massague, 1998). Activation of Smad3, but not Smad2, is one of the key and absolute necessary mechanisms required for Angiotensin (Ang) II-induced vascular fibrosis. This is because the Ang II-induced Smad3/4 promoter activities and collagen matrix expression are abolished in VSMCs null for Smad3 but not Smad2. There are several phases that promote Smad signaling in Ang II. During the first phase, Ang II directly activates an early Smad signaling pathway at approximately 15 to 30 minutes. During the second phase, Ang II subsequently activates the late Smad2/3 signaling pathway at 24 hours. This pathway is TGF-β1 dependent, as it can be blocked by the anti-TGF-β antibody (Wang W et al., 2006).

2.4 TGF-β1 and the renin-angiotensin system

Ang II promotes sodium retention, cell growth and fibrosis, in addition to the classical effects it has on blood pressure and fluid homeostasis. Since it is well known that Ang II enhances TGF-β1 expression, TGF-β1 signaling pathways, and cardiac remodeling, which includes cardiac hypertrophy and cardiac fibrosis, the activation of TGF-β1 is considered to be closely associated with an Ang II excess (Ruiz-Ortega et al., 2007).

In the hypertrophic myocardium, TGF-β1 tissue levels are markedly increased after cardiac stress loading, such as with an Ang II excess (Ikeda et al., 2005; Yagi et al., 2008). Furthermore, the stimulus that is associated with the increase in the activity of Ang II in heart tissue can repeatedly trigger the expression of TGF-β1 and lead to continual injury. Therefore, it is thought that there is a biologically rich and complex interaction that occurs between the renin-angiotensin system (RAS) and TGF-β1 in which both act at various points to regulate the actions of the other. This interaction might be the key to understanding the vital roles that RAS and TGF-β1 play in EH development.

Another interplay between RAS and TGF-β1 involves the level of aldosterone. Ang II normally stimulates the production and release of aldosterone from the adrenal gland. Conversely, TGF-β1 suppresses production and strongly blocks the ability of Ang II to stimulate aldosterone by reducing the number of Ang II receptors expressed in the adrenal gland (Gupta et al., 1992). Furthermore, it has been shown that TGF-β1 can block the effects of aldosterone on sodium reabsorption in cultured renal collecting duct cells (Husted et al., 1994). It has also been shown that after an infusion of aldosterone into rats with a remnant kidney, there is an increase in blood pressure, proteinuria, and glomerulosclerosis along with a neutralization of the beneficial effects of the Ang II blockade (Greene et al. 1996). Although the mechanism of aldosterone's pathological effects is still unknown, it might be due to stimulation of TGF-β1 production in the kidney.

EH is the most common cause of hypertension. The second most common cause of hypertension is primary aldosteronism (PA), which has recently been implicated in the alterations of the immune system and progression of cardiovascular disease. As compared to EH controls, PA patients have lower TGF-β1 levels (17.6+/-4.1 vs. 34.5+/-20.5 pg/ml, $p<0.001$). In addition, TGF-β1 levels were shown to exhibit a remarkable correlation with the serum-aldosterone/plasma-renin-activity ratio in the total group (PA+EH) (Carvajal et al., 2009). Therefore, a chronic aldosterone excess in PA patients appears to modify the TGF-β1 levels. If so, this could lead to an imbalance in the immune system homeostasis, thereby leading to an early proinflammatory cardiovascular phenotype in these patients.

2.5 TGF-β1 and endothelin 1

Endothelin-1 (ET-1) is a vasoconstricting peptide that is produced primarily in the endothelium and which seems to play a key role in vascular homeostasis, tissue remodelling and fibrogenesis. These effects are mediated via two receptor types, ET_A and ET_B. In blood vessels, ET_A receptors are found in VSM cells, whereas ET_B receptors are mainly localized on endothelial cells and, to some extent, in VSM cells and macrophages. ET-1, which acts predominantly via the ET_A receptors, promotes vasoconstriction, cell growth, adhesion, fibrosis, and thrombosis. TGF-β1 induces ET-1 expression by a functional cooperation between Smads and activator protein-1 via activation of the Smad signaling pathway (Yang et al., 2010). Moreover, TGF-β1 enhances NO generation in the endothelium, which in turn suppresses TGF-β1 production. When NO production is impaired, such as with hypertension, aging, and other systemic diseases, unopposed excess vascular TGF-β1 production results in reduced vascular compliance and augmented peripheral arterial constriction and hypertension. Thus, NO functions as both a regulator for TGF-β1 production and as a physiological antagonist of ET-1.

Data from clinical trials have already demonstrated significant blood pressure lowering effects that occur after the combined use of ET_A-ET_B receptor blockers. ET-1 receptor blockade diminishes TGF-β production in cardiac, vascular, and renal tissues (Kowala et al., 2004). While the role that ET-1 plays in normal cardiovascular homeostasis and in mild EH is still unclear, plasma ET-1 levels are increased in EH patients with atherosclerosis or nephrosclerosis when compared with patients with uncomplicated EH (Lariviere&Lebel, 2003). Thus, targeting the endothelin system might potentially be an important therapeutic treatment for EH, particularly for preventing target organ damage and managing cardiovascular disease.

2.6 TGF-β1 and organ damage-induced hypertension

Several in vitro and in vivo studies have confirmed the role of TGF-β1 in the development of heart muscle hypertrophy. An in vivo model has demonstrated there is an increase in mRNA and protein levels of TGF-β1 in the cardiomyocytes of hypertrophied heart (Kobayashi et al., 2001). Overexpression of TGF-β1 in transgenic mice has been shown to result in cardiac hypertrophy that is characterized by both interstitial fibrosis and hypertrophic growth of the cardiomyocytes (Rosenkranz, et al., 2002). These findings indicate that local production of TGF-β1 in the hypertrophic myocardium and the link between the RAS and TGF-β1 signaling pathway are involved in the hypertrophic response.

Hypertensive subjects can be considered to be at a higher risk of end-stage renal disease (ESRD). Scaglione et al. evaluated the relationship between circulating TGF-β1 and the progression of renal damage in a population of EH subjects. They evaluated the albumin excretion rate in EH patients and found there was a strong relationship between the progressive increase of TGF-β1 levels and the progression of renal damage (Scaglione et al., 2002). Thus, it is possible that TGF-β1 overproduction may be the pathogenetic mechanism for the excess burden of hypertension and hypertensive renal damage. August et al. demonstrated that African Americans with ESRD had higher circulating levels of TGF-β1 protein as compared to Caucasians with ESRD. They also found that hyperexpression of TGF-β1 was more frequent in African Americans with EH than in Caucasian Americans (August et al., 2000). Based on their findings, TGF-β1 is a treatment target that might be

especially pertinent in hypertensive African Americans. In addition, anti-TGF-β1 therapy could also be efficacious in preventing or slowing the progression of target organ damage.

2.7 TGF-β1 gene polymorphisms, hypertension and organ damage

The *TGF-β1* gene, is located in the 19q13 chromosome and has 7 exons and 6 introns. Molecular biology research has confirmed that there are gene variations and polymorphisms in the *TGFB1* that are associated with EH. A meta-analysis that was performed in the Chinese population and which included 5 separate studies with 2708 subjects showed there was a relationship between the +869T/C polymorphism of *TGFB1* and EH. The pooled odds ratio (OR) for the CC/TC+TT genotype was 2.50, while the pooled OR for the frequency of the C allele was 1.43 (Yan-Yan, 2011). In Japanese individuals, Yamada et al. found that the frequency of the C allele in hypertensive women was higher than that seen in normotensive women, although there were no significant differences noted between hypertensive and normotensive men (Yamada et al., 2002). This research demonstrated that the association of the *TGFB1* polymorphism and EH was most likely influenced by the gender factor. Another study suggested that the prevalence of the TC or CC genotypes of the +29T/C polymorphism in the gene was significantly higher in hypertensives versus normotensives. In addition, there was a higher prevalence of subjects with microalbuminuria and left ventricular hypertrophy (LVH) in hypertensives having these genotypes as compared to the hypertensives with the TT genotype (Argano et al., 2008).

To investigate the linkage between the *TGFB1* polymorphism and the progression of atherosclerosis, Sie et al. conducted a population-based study that investigated five functional polymorphisms in *TGFB1* (-800 G/A, -509 C/T, codon 10 Leu/Pro, codon 25 Arg/Pro and codon 263 Thr/Ile) in relation to the arterial stiffness (pulse wave velocity (PWV), distensibility coefficient (DC) and pulse pressure (PP)). However, neither these polymorphisms nor the haplotypes were associated with the PWW, DC or PP (Sie et al., 2007). Conversely, the C allele of TGFB1 rs4803455 in an elderly Chinese man was shown to be significantly associated with the prevalence of carotid plaque (Deng et al., 2011).

As compared to Caucasian Americans, African Americans have a higher incidence and prevalence of hypertension and hypertension-associated target organ damage, which includes hypertensive nephrosclerosis. Suthanthiran et al. demonstrated that TGF-β1 protein levels were the highest in African American hypertensives, and that the TGF-β1 protein as well as the TGF-β1 mRNA levels were higher in hypertensives when compared to normotensives (Suthanthiran et al., 1998) They also showed that the proline allele at codon 10 of *TGFB1* was more frequently observed in African Americans as compared with Caucasian Americans. In addition, its presence was also associated with higher levels of TGF-β1 mRNA and protein. These findings suggest that TGF-β1 hyperexpression might be a risk factor for hypertension and hypertensive complications, in addition to being the basis of the mechanism for the excess burden of hypertension in African Americans.

2.8 TGF-β1 and antihypertensive treatment

Laviades et al. reported that the efficient blockade of the AT_1 receptors that is observed when using losartan is associated with the inhibition of TGF-β1, normalization of collagen

type I metabolism, and reversal of left ventricular hypertrophy and microalbuminuria in hypertensive patients (Laviades et al., 2000). As a similar effect has been reported for captopril, this suggests that both angiotensin converting enzyme inhibitor (ACEI) and Ang II receptor blocker (ARB) attenuate the TGF-β1 expression (Sharma et al., 1999). Furthermore, although high glucose has also been shown to increase the production of Ang II and TGF-β1, both ACEI and ARB attenuated the increase in TGF-β1 production and reduced the cell proliferation caused by exposure to high glucose. These effects were greater when a combination of the two drugs were used (Kyuden et al., 2005). Scaglione et al. evaluated the effects of 24 weeks of losartan and ramipril treatment, both alone and in combination, on the circulating TGF-β1 and left ventricular mass (LVM) in EH patients. Their results showed that the absolute and percent reduction in TGF-β1 and LVM were significantly higher in the combined versus the individual losartan or ramipril groups. Thus, these findings indicate there is an additional cardioprotective effect provided by the dual blockade of renin-angiotensin in EH patients (Scaglione et al., 2007).

Hallberg et al. determined the impact of the + 915G/C polymorphism of *TGFB1* on the response to antihypertensive treatment. In a randomized double-blind study designed to treat EH patients for 48 weeks with either the AT_1 receptor antagonist irbesartan or the β1-adrenoceptor blocker atenolol, they examined the association between the TGF-β1 genotype and LVM regression in patients that had been echocardiographically diagnosed with LVH. Irbesartan-treated patients who were carriers of the C allele, which is associated with a low expression of TGF-β1, responded with a markedly greater decrease in the LVM index (LVMI) as compared to subjects with the GG genotype (adjusted mean change in LVMI -44.7 g/m2 vs. -22.2 g/m2, $p = 0.007$). This decrease occurred independent of the blood pressure reduction. However, no association was noted between the genotype and the change in LVMI in the atenolol group. Therefore, they concluded that the *TGF-β1* + 915G/C polymorphism was related to the change in the LVMI in response to the antihypertensive treatment with the AT_1 receptor antagonist irbesartan (Hallberg et al., 2004).

Based on these findings and the observations that ACEI and ARB are able to reduce Ang II-mediated stimulation of the TGF-β1 production, treatments using these agents might be efficacious in preventing or slowing the progression of target organ damage in EH, especially in those patients who have LVH or hyperglycemia. Moreover, based on data presented above, it can be speculated that greater disease reduction could perhaps be achieved if TGF-β1 rather than blood pressure was the therapeutic target.

3. Emilin 1

3.1 EMILINs family

EMILINs are a family of proteins of the extracellular matrix. The first protein of the family, initially named gp115, was isolated from chicken aorta under harsh solubilizing conditions. This protein was particularly abundant in the aortic tissue, and further immunohistochemical studies also showed it to be strongly expressed in blood vessels and in the connective tissues of a wide variety of organs, particularly in association with elastic fibers (Colombatti et al., 1987). At the ultrastructural level, the molecule was detected in elastic fibers, where it was located at the interface between the amorphous core and the surrounding microfibrils (Bressan et al., 1993). On the basis of this finding, the protein was

named EMILIN (elastin microfibril interface-located protein). Cloning of the cDNA of chicken EMILIN lead to the isolation in both human and mouse genes, with a total of three genes having been identified in humans and mice at the present time. The cardiovascular system has been demonstrated to be the major site of expression for the *EMILIN* genes (Braghetta et al., 2004).

EMILINs share four protein domains, the C-terminal C1q domain, collagenous domain, coiled-coil domain and N-terminal cysteine-rich domain (EMI domain) (Colombatti et al., 2000). There are also unique domains that are not shared by the EMILIN proteins. For example, EMILIN1 has two leucine zipper regions, multimerin has an endothelial growth factor-like domain, and EMILIN2 contains a proline-rich domain. This domain organization suggests that there are some shared and some specific functions for each of these EMILIN proteins.

3.2 EMILIN1 and hypertension

EMILIN1 was originally isolated form the aorta and is intimately associated with elastic fibers and microfibrils in the blood vessels, as well as in the connective tissue of other organs. EMILIN1 is a monomer when it is within the cells, but upon secretion, it oligomerizes via the formation of disulfide bonds. EMILIN1 appears to be more slowly secreted than other ECM components, although the implication of this is unclear (Colombatti et al., 2000). The function of EMILIN1 remained unknown until the gene was finally disrupted in mice. Although EMILIN1 knockout mice are fertile and have no obvious abnormalities, histological and ultrastructural examinations have shown there are alterations of the elastic fibers in the aorta and skin. Formation of elastic fibers by mutant embryonic fibroblasts in cultures has also been found to be abnormal (Zanetti et al., 2004). These mice develop larger lymphangiomas as compared to Wild type mice. Lymphatic vascular morphological alterations in these mice are also accompanied by functional defects, such as mild lymphedema, a highly significant drop in lymph drainage, and enhanced lymph leakage (Danussi et al., 2008).

In 2006, Zacchigna et al. found that *Emilin1* deficient mice become hypertensive (systolic blood pressure: 120±2 versus 101±1, n=46 per group, $P<0.01$), in addition to exhibiting an increased peripheral vascular resistance and a reduced vessel size, all of which were independent of the cardiac output. Strikingly, after inactivation of a single TGF-β allele, the high blood pressure in the mice returned to normal levels. A further study revealed that EMILIN1 inhibits TGF-β signaling by specifically binding to the proTGF-β precursor, thereby preventing its maturation by the furin convertases in the extracellular space (Zacchigna, et al., 2006). This study highlighted the importance of the relationship between EMILIN1 and TGF-β availability in the pathogenesis of hypertension. EMILIN1 may inhibit TGF-β by several different mechanisms. First, it is possible that it could interfere with TGF-β secretion or maturation, or second, it could prevent the presentation or the interaction of the TGF-β ligands with the cognate receptors. Finally, it could also be possible that it acts by sequestering either the immature or mature ligand (Zacchigna, et al., 2006). Therefore, further studies will need to be undertaken that conclusively prove that: 1) EMILIN1 modulates TGF-β availability during the development of the cardiovascular system, 2) EMILIN1 is associated with the pathogenesis of hypertension, and 3) TGF-β maturation is linked to the blood pressure homeostasis that has been identified in animal studies. If these

future studies do lead to the discovery of the genetic susceptibility of *EMILIN1* gene to hypertension, this will ultimately lead to a better understanding of the mechanism of human hypertension.

3.3 EMILIN1 gene polymorphisms and EH

The human *EMILIN1* gene, which encodes EMILIN1, consists of 955 amino acids and is located on chromosome 2p23.3-p23.2, which overlaps with the promoter region of the ketohexokinase gene (Doliana et al., 2000). The gene is quite small and consists of approximately 7.3 kilo base-pairs that contain eight exons, and which are interrupted by seven introns. In a previous investigation of the association of the *EMILIN1* gene polymorphisms and EH, we genotyped a total of 287 EH patients and 253 age-matched controls for five single-nucleotide polymorphisms (SNPs) used as genetic markers for the human *EMILIN1* gene (rs2289408, rs2289360, rs2011616, rs2304682, and rs4665947). We confirmed that rs2289360, rs2011616, and rs2304682, as well as the haplotype constructed using rs2536512, rs2011616, and rs17881426 were useful genetic markers of EH in Japanese men (Shimodaira et al., 2010). In a Mongolian population, the rs2304682 locus in *EMILIN1*, as well as the haplotypes G-G constructed using rs3754734 and rs2304682, appeared to be associated with the susceptibility of EH. In addition, rs2304682 may also be associated with the level of the diastolic blood pressure (Mi et al., 2011). Conversely, Shen et al. reported finding no significant association between the *EMILIN1* gene and EH, although the interaction of age and genotype variation of rs3754734 and rs2011616 might increase the risk of EH in the northern Han Chinese population (Shen et al., 2009). In order to definitively determine if there is an association between the genetic variation of the *EMILIN1* gene and increases in the blood pressure, further studies that investigate the role of the *EMILIN1* gene in vascular development and blood pressure homeostasis will need to be undertaken. At the present time, however, there have yet to be any reports of human hereditary diseases that are involved with EMILINs. Therefore, the morphological abnormalities revealed in this study constitute the first potential hallmark of EMILIN1 insufficiency, which may prove to be helpful in identifying heritable diseases induced by mutations of this gene in the future.

4. Conclusion

Many studies over the last decade have attempted to elucidate the important roles of TGF-β1 and EMILIN1 in the maintenance of normal blood vessel wall architecture in humans. While most of the results reviewed here are consistent with the concept that TGF-β1 and EMILIN1 have similar roles in the vasculature of humans and rodents, direct and conclusive evidence has yet to be found. However, this is not all that surprising when one considers the difficulty of probing complex systems in humans. Although interventional experiments are commonplace in animal models, almost all without exception are impossible to perform in the regulatory systems in the human vasculature. From a therapeutic point of view, understanding the complexities of the interplay between the TGF-β1 signaling pathway and the development of EH are matters of great importance. For the most part, strategies that decrease TGF-β1 activity may very well be able to protect against hypertension and hypertensive organ damage. Once definitive information on the TGF-β1 signaling pathway and human hypertension becomes available, novel therapeutic approaches that modulate the biological actions of TGF-β1 might become available for use in EH patients.

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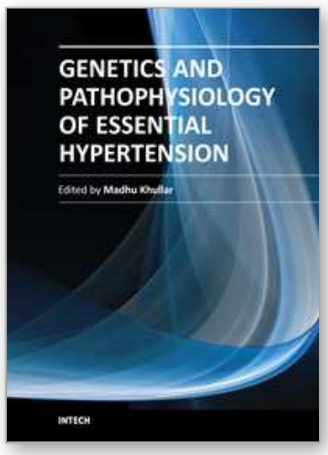

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This book, authored by renowned researchers in the field of Hypertension Research, details the state of the art knowledge in genetics, genomics and pathophysiology of Essential hypertension, specifically the genetic determinants of hypertension and role of gene variants in response to anti-hypertensive therapy. Two chapters describe mitochondrial mutations in Essential hypertension and in hypertension associated Left ventricular hypertrophy, one chapter reviews in detail the global gene expression in hypertension, and an up to date treatise on pathophysiology of resistant hypertension is detailed in another chapter. Other topics included in the book are end organ damage, baroreceptor sensitivity and role of music therapy in essential hypertension.

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
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