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Mini Review

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ACE /ACE2 Gene Polymorphisms and Cardiovascular Diseases

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Abstract

This minireview tries to describe and summarize some substantial knowledge about association of frequent polymorphisms in two main enzymes of the renin-angiotensin-aldosterone system with cardiovascular system and risk factors for cardiovascular diseases.

Keywords: RAS; ACE; ACE2; cardiovascular diseases

Renin-Angiotensin-Aldosterone System (RAS) In Larger Frame

Angiotensin converting enzyme (ACE) and angiotensin converting enzyme 2 (ACE2) are substantial enzymes of both-pressor and ant pressor- branches of the renin angiotensin aldosterone system (RAS). From the physiological point of view, the system is responsible for basic cardiovascular regulation by changes of volume as well as pressure characteristics. Now, it is known that the RAS is composed of two axes with mostly opposite functions. The first axis -pressor- is formed by the enzyme ACE, with Ang II as the end product, and the AT1 receptor as the main effector mediating the biological actions of Ang II. The second axis -depressor-is characterized by ACE2-mediated production of Ang-(1-7), with Mas receptor as the main effector. Activation of the ACE2/Ang- (1-7)/ Mas axis leads to depressor, vasodilation, anti-inflammatory and antifibrotic trends [1]. ACE plays a significant role in fluid and electrolyte balancing, blood pressure regulation, cardiovascular system development and vascular remodeling [2]. ACE has a role in innate and as well as adaptive immune responses as it is seen to modulate macrophage and neutrophil function. These effects are supported when there is an overexpression of ACE by these cells. Macrophages with ACE overexpression have been found to be more effective against tumors and infections. Neutrophils that overexpress ACE have been shown to be able to increase superoxide production. Also, major histocompatibility complex (MHC) class I and MHC class II peptides expression was proved to be affected by ACE [3].

ACE

The enzyme (ACE, EC 3.4.15.1) was isolated in 1956. Two forms of the enzyme can be distinguished in humans, a somatic form (sACE), found in several tissues, and a smaller tACE, found exclusively in testes. Both forms function at the cell surface and hydrolyse circulating peptides. A soluble form of ACE, derived via the action of a secretase on the membrane form, is also present in body fluids. The gene for human sACE is composed of 26 exons, the testicular ACE (tACE), is transcribed from exons 13 to 26. It has been suggested that the sACE gene could result from gene duplication of

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tACE. Somatic ACE is associated with two zinc atoms. The structure of tACE is identical to the C-domain of somatic ACE, with exception for a particular N-terminus and only one zinc atom in the single site [4]. I/D ACE polymorphism was detected in 1990 by Rigat [5].

A polymorphism characterized by the insertion or deletion of a 287-bp Alu repeat sequence in intron 16 of the angiotensin-converting enzyme gene determines about half the serum angiotensin-converting enzyme level variability among individuals. The deletion polymorphism is associated with higher levels of angiotensin-converting enzyme and perhaps with a greater risk of cardiovascular diseases. The ancestral D allele of ACE gene is supposed to be not only plastic in response to its environmental circumstance (temperature, humidity) but also presents a striking geographic distribution showing the evidence of 'signatures of selection' by climate factors [6]. In 1999, our group published how interaction between polymorphism I/D ACE and ABO blood group system could significantly modify mean values of blood pressure and a phase shift of 24 h BP periods corrected for sex and BMI in Czech population [7]. Insertion/deletion (I/D) polymorphism of the gene encoding angiotensin converting enzyme (ACE) is a controversial risk factor for heart diseases (HDs). ACE I/D polymorphism has been reported to be associated with various cardiovascular diseases. However, some studies have presented conflicting results. The association between ACE I/D polymorphisms and the risk of coronary HD (CHD), coronary artery disease (CAD), and myocardial infarction (MI) was studied using a metanalytic approach. The meta-analysis included 12,533 cases and 20,726 controls from 75 case-control studies. The D allele of ACE was found to be significantly associated with increased risk of HDs. The D allele of ACE was significantly associated with an increased risk of HDs in the Asian and European groups but not in the American group. In addition, in all three subgroups (CHD, CAD, and MI), the D allele of ACE was found to be significantly associated with increased risk of disease [8]. Another metanalysis of 118 studies (43 733 cases with CAD and 82 606 controls) found association of I/D ACE genotype and CAD. Also, significant association for myocardial infarction, diabetes mellitus, male sex, white race, East Asian subjects, and Turkish subjects were found. There was a differential magnitude of effect in large vs small studies [9]. But, even in metanalysis study controversial results can be observed. Meta analysis of seventeen case-control studies with a total of 5576 participants including 2453 cases with heart failure (HF) and 3123 controls showed no association between I/D ACE polymorphism and heart failure i any genetic model. Similarly, analyses for ischemic HF (IHF) and HF because of dilated cardiomyopathy (DHF)don´t reach a significant association between ACE I/D polymorphism and HF [10]. Another meta-analysis provided good evidence suggesting that the D allele of I/D ACE polymorphism was a genetic risk factor for hypertrophic cardiomyopathy [11]. Apart from tACE and sACE, two studies published in 2000 discovered that humans also express a homologue of ACE called ACE2 [12, 13].

ACE2

ACE2 (EC 3.4.17.23) is expressed in most human tissues and cell types as a type I integral membrane protein. The soluble forms can be formed by the action of a disintegrant and metalloproteinase (ADAM)-17. The expression levels of ACE2 are highest in the small intestine, testis, kidneys, heart, thyroid and adipose tissue; intermediate in the lungs, colon, liver, bladder and adrenal glands; lowest in the blood, spleen, bone marrow, brain, blood vessels and muscle [14]. The ACE2 gene is located on X chromosome, with about 3328 bases, 20 introns and 18 exons. The ACE2 emerges as a potent negative regulator of the renin-angiotensin-aldosterone system (RAS). Targeting angiotensin II, ACE2 exhibits a protective role in the cardiovascular system and many other organs [15]. ACE2 substantially participates in the absorption of amino acids in the kidney and gut [16, 17]. ACE2 is expressed in endothelial cells and smooth muscle cells in many organs [18]. The type I and type II pneumocytes were found to synthetize ACE2 [18]. Because the physiological function of ACE2 is opposite to that of ACE, it is speculated that ACE2 plays a protective role in cardiovascular disease [19]. Considering participation of all important organs (brain, heart, lungs, liver, GIT, kidneys, bone marrow) in the whole-body regulation of RAS system, it is questionable what exactly levels of ACE2 (as well as of ACE) reflects at any moment of cardiovascular system regulation. But higher levels of plasma ACE2 were associated with greater risk of death, due to both cardiovascular and non-cardiovascular reasons, may be as a result of dysregulation of the whole RAS system. Also, male sex, higher blood pressure, smoking, higher BMI, and older age were all associated with higher levels of circulating ACE2 concentration. The associations of polymorphisms in the angiotensin-converting enzyme 2 (ACE2) gene with cardiovascular risk have not been fully determined [20]. A significant association of ACE2 gene polymorphisms (rs4646156 and rs4646174) with central pulse pressure (PP) measured coronagraphically was found in Czech patients with cardiovascular diseases [21]. The values of PP were higher in women; significant differences among five genotypes in the population (X-linked heredity of ACE2) were distinguishable which could be of great importance in severe clinically ill patients. Testing ACE2 genotypes as possible independent predictors of central PP using multivariate analysis was performed.

The most predictable model included brachial PP, age, ACE2 rs4646174 genotypes and the number of affected coronary arteries. Single nucleotide polymorphisms (SNPs) in ACE2 were genotyped in participants of the prospective MORGAM study (n = 5092) from five cohorts: ATBC, FINRISK, Northern Sweden, PRIME/Belfast and PRIME/France. The A allele of the rs2285666 polymorphism was significantly associated with the risk of cardiovascular death in female subjects. Vangjeli The current COVID-19 pandemic has resulted in over one million infected worldwide and thousands of deaths. The virus binds and enters through angiotensin-converting enzyme 2 (ACE2) receptor. COVID-19 can lead to systemic inflammation, multiorgan dysfunction, and critical illness. The cardiovascular system can be also affected by myocardial injury, myocarditis, acute myocardial infarction, heart failure, dysrhythmias, and venous thromboembolic events [22]. It is questionable whether double genotypes and/or haplotypes evaluated together for ACE and ACE2 polymorphisms should be clinically useful. An important association for the combination of I/D ACE DD genotype with G8790A ACE2 GG genotype (DD/GG) on Brazilian female subjects was referred with a significant

7-times increased risk of hypertension compared to individuals carrying the II/GG genotype in Brazilian population [23]. The ACE/ACE2 genotypic profile II/A in I/D ACE and G8790A ACE2 double genotype was shown to be a protective genotype against the worsening of COVID-19 conferring almost four times less chance of having a worse prognosis in the evolution of the disease [24]. Finally, the necessity to continue in complicated clinical research must be accented which will lead to complete understanding of genetic predisposition to cardiovascular disease.

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Conflict of Interest

No Conflict of Interest.

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