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Proteomics in cardiovascular diseases: Unveiling sex and gender differences in the era of precision medicine

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ABSTRACT

Cardiovascular diseases (CVDs) represent the most important cause of mortality in women and in men. Contrary to the long-standing notion that the effects of the major risk factors on CVD outcomes are the same in both sexes, recent evidence recognizes new, potentially independent, sex/gender-related risk factors for CVDs, and sex/gender-differences in the clinical presentation of CVDs have been demonstrated. Furthermore, some therapeutic options may not be equally effective and safe in men and women. In this context, proteomics offers an extremely useful and versatile analytical platform for biomedical researches that expand from the screening of early diagnostic and prognostic biomarkers to the investigation of the molecular mechanisms underlying CDVs. In this review, we summarized the current applications of proteomics in the cardiovascular field, with emphasis on sex and gender-related differences in CVDs.

Significance: Increasing evidence supports the profound effect of sex and gender on cardiovascular physio-pathology and the response to drugs. A clear understanding of the mechanisms underlying sexual dimorphisms in CVDs would not only improve our knowledge of the etiology of these diseases, but could also inform health policy makers and guideline committees in tailoring specific interventions for the prevention, treatment and management of CVDs in both men and women.

1. Introduction

Cardiovascular diseases (CVDs) are the world's leading cause of morbidity and mortality, accounting for > 17 million deaths annually [1], and cause immense health and economic burdens [2,3]. In line with the recommendations of the World Health Organization (WHO), the principal health organizations in the field of heart diseases and stroke (such as the American Heart Association and the European Society of Cardiology) formulated recommendations to drive organizational priorities and guide actions to prevent CVDs in clinical practice [4,5]. In accordance with the strategic view of these recommendations, to achieve the goal of significantly reducing deaths attributable to CVDs continued emphasis is needed on the treatment and control of health behaviors and risk factors at both the population and the individual level [2,5]. In the era of precision medicine, the key challenge is to bridge the gaps in our knowledge about sex- and gender-related differences in the pathophysiology of the cardiovascular system, since increasing evidence supports the notion that an individual's sex is one of the most important modulators of disease risk and response to treatment [6–8] (Box 1).

Indeed, a large amount of correlative data unveils the existence of sexual diversities in human physiology and differential susceptibility to a wide variety of pathologies including CVDs [9,10]. Beyond environmental and social differences between men and women (e.g., occupational hazards, lifestyle, social stresses, access to healthcare) that can contribute to gender differences in CVDs, sex hormones have long been found to account for some sex-related differences in CVDs, and some molecular mechanisms mediating these effects have recently been elucidated [8,10,11]. Moreover, sex chromosomes are beginning to be recognized as important determinants of sexual dimorphism in the development of CVDs, independent of sex hormones [8,10–12]. In this Review, we consider the evidence for sex and gender differences in CVDs and summarize the proteomic research that has been conducted in this field.

2. Sex-specific and gender-specific cardiovascular research

CVDs have long been considered as male diseases, an assumption

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Box 1
Sex vs. gender.

Sex and gender are different constructs. According to the WHO, sex "*refers to the set of biological characteristics that define humans as female or male*"; it is primarily associated with physical and physiological features including chromosomes, gene expression, hormone levels, and reproductive/sexual anatomy. Gender encompasses biology but is also influenced by experience and environment: it "*refers to the socially constructed roles, behaviors, activities, and attributes that a given society considers appropriate for men and women*"; it influences the distribution of power and resources, including access to healthcare. Sex and gender influence each other through complex interactions. Both sex and gender are critical variables in preclinical and clinical research.
http://www.who.int/reproductivehealth/topics/sexual_health/sh_definitions/en/
http://www.who.int/gender-equity-rights/understanding/gender-definition/en/

that stems largely from observations that CVDs in women develop later in life than in men, and the misperception that CVDs among women are not as severe as they are in men [13]. In line with this view, until recently cardiovascular research was predominantly conducted in men and it was assumed that clinical approaches based on research findings involving men were equally relevant for women [13]. However, a growing body of evidence has progressively revealed the importance of CVDs in women and has fostered the awareness of sex- and gender-related differences in the occurrence, management and outcomes of CVDs [13]. Marked progress has been made in the involvement of women in large-scale population studies and clinical trials. Nevertheless, several gaps in our understanding of sex- and gender-related diversities in cardiovascular health still persist. Moreover, the use of female animals, cells, or tissues, and sex-based reporting in preclinical investigations have not been equally implemented [14], in spite of the publication of a planned policy from the U.S. National Institutes of Health (NIH) to balance sex in cell and animal studies [15]. In this regard, it is important to highlight the value of preclinical studies for understanding the molecular bases of sex differences, since such studies: 1) enable scientists to take full advantage of the power of molecular genetics and 'omics technologies; 2) allow the control of variables such as diet, environment, exercise; and 3) offer the opportunity to quantify the extent of sex or gender contribution to the biological outcome, since in experimental animals gender has limited impact [9].

3. Sex and gender differences in CVD risk factors

Most of the traditional risk factors for CVDs, including elevated blood pressure, dyslipidemia, excess body weight and obesity, diabetes, and cigarette smoking, are similar between men and women, but for some of them the impact differs between the sexes; furthermore, recent evidence has emerged that recognizes new, potentially independent female-specific risk factors (Fig. 1) [8,16].

3.1. Major risk factors affecting both men and women

3.1.1. Elevated systolic blood pressure

Elevated systolic blood pressure (SBP) is one of the leading risk factors for global mortality and for CVDs. In 2015, the prevalence of raised blood pressure was around 20% in females aged 18 and over and around 24% in males [17]. Studies have reported conflicting results on whether the association between increments in SBP and CVDs differs between sexes [16]. A pooled analysis carried out in 2013, including data from prospective cohort studies on > 1.2 million individuals and over 50,000 cardiovascular events, found that every 10 mmHg increment in SBP was associated with a 15% increased risk of coronary heart disease (CHD) and a 25% increased risk of stroke in both men and women, indicating a similar impact of hypertension on cardiovascular outcomes in both sexes [18]. In contrast, results of a recent meta-regression analysis of US population-based studies indicate that women experienced a 10% greater risk in CVDs per 10 mmHg increment in SBP than men, after adjusting for age and baseline SBP [19].

3.1.2. Dyslipidemia

Raised total cholesterol (TC) is estimated to account for over 2.6 million deaths (4.5% of total) worldwide every year [20]. The prevalence of elevated TC is similar in men and women [20] and studies addressing the possible sex/gender-specific effects of TC on CVD risk have reported inconsistent results [21]. The first systematic meta-analysis evaluating the impact of TC on CVD risk in women compared with men included data from over one million individuals and > 20,000 CHD and 16,000 stroke events [21]. This analysis found that for every 1-mmol/L increment in TC, the risk of CHD increased by 20% in women and by 24% in men, indicating essentially a similar TC-related risk of CHD in both sexes [21].

In population studies, high-density lipoprotein cholesterol (HDL-C) is inversely related to the risk of myocardial infarction and death [22].

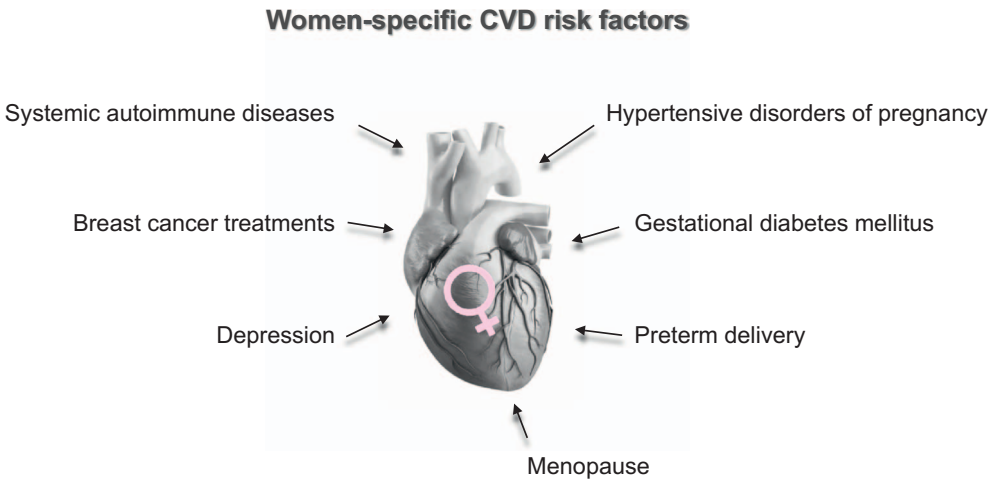

Fig. 1. Women-specific CVD risk factors. Women-specific conditions to consider in risk evaluation, diagnosis and treatment of CVDs include hypertensive disorders of pregnancy, gestational diabetes mellitus, preterm delivery, menopause, systemic autoimmune disease, breast cancer treatments, and depression.