The interplay between genetics, epigenetics and environment in modulating the risk of coronary heart disease

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In the second decade of the 21st century, coronary heart disease (CHD) remains the leading cause of morbidity and mortality worldwide (1). Despite the overall prevalence of this condition has favourably declined over the last 10 years, the death rate remains high, accounting for approximately 1 of every 7 deaths in the United States (2), thus paving the way to additional research aimed at identifying reliable means of prevention and clinical management.

The acute coronary syndrome develops through a pathophysiological continuum, beginning with transitory myocardial ischemia and culminating in overt necrosis of contractile myocardial tissue and impaired heart function (3). Despite the pathogenesis and clinical presentation may differ between the various types of acute myocardial infarction (AMI) (4), coronary atherosclerosis represents the leading aetiological factor in most cases of myocardial ischemia (i.e., type 1 AMI). Briefly, a pre-existent atherosclerotic plaque may undergo rupture, ulceration, fissuring, erosion or dissection, so triggering the formation of intraluminal thrombosis in coronary arteries, decreased blood flow and resulting in myocardiocyte necrosis (3).

As many other prevalent human disorders such as cancer, diabetes and venous thromboembolism, myocardial infarction is conventionally regarded as a complex, multifactorial disease (5). More specifically, when a subject is unfortunate enough to accumulate one or more inherited or acquired risk factors, the individual risk is propelled over such a threshold that may trigger the onset of AMI. Despite several lines of evidence were brought to attest that genetic, epigenetic and environmental factors strongly interplay in the pathogenesis of CHD, large prospective studies which reliably correlated those different factors are almost lacking (6). This gap has been recently filled by a large investigation, which pooled data from three prospective studies [Atherosclerosis Risk in Communities (ARIC) study; Women's Genome Health Study (WGHS); Malmö Diet and Cancer Study (MDCS)], totaling 51,425 subjects for whom a variety of genetic [50 single-nucleotide polymorphisms (SNPs)] and lifestyle factors (current smoking, obesity, physical inactivity and unhealthy diet pattern) were independently related to the susceptibility of CHD (7). The most substantial information has emerged from the calculation of the 10-year cumulative incidence rate of coronary events, showing that such risk varies between 1.2–3.1% in subjects with favorable lifestyle and no genetic risk factors, up to 4.6–10.7% in those having unfavorable lifestyle and high genetic risk. Unlike the aggregate data, the 10-year cumulative risk attributable to either unfavorable lifestyle alone (1.8–5.8%) or high genetic risk alone (1.2–5.1%) was found to be more than 2-times lower. Overall, the combination of unfavorable genetic and lifestyle profiles conferred a 1.7–2.3 higher risk of CHD than each variable alone, so clearly confirming that genes and environment strongly interplay to determine an excess risk of future coronary events, at least in part by modulating epigenetic mechanisms related to metabolism, inflammation and vascular involvement.

The important results of this study disclose intriguing perspectives into putative domains of CHD management. Despite it has been known for decades that the risk of CHD

has a strong inherited component (e.g., family history is still regarded as one of the major predisposing risk factors for cardiovascular disease) (8), genetic screening for identifying the presence of a discrete number of relevant SNPs may hence be offered to selected categories of individuals, especially those with a familiar history of premature CHD, as increasingly feasible by incessant development and commercialization of high-throughput SNP genotyping platforms. Although genetic and epigenetic therapy for CHD is still in its infancy (9), the early identification of individuals with a high-risk genetic profile may help targeting modifiable risk factors, by timely promoting lifestyle interventions such as smoking cessation, weight reduction, physically active behaviors and healthy dietary habits. In the meanwhile, it may also be advisable to plan cost-effectiveness analyses to establish whether the incremental cost of genotyping may be actually balanced by predictable savings due to preventing, or at least delaying, the onset of future coronary events. One final consideration concerns the impact of environmental changes in the burden of CHD. Many exposure scenarios have been strongly associated with epigenetic changes, ultimately promoting the development of pro-atherosclerotic profiles (10). Accumulating evidence suggests that pollutants and climate changes (e.g., global warming) generate a kaleidoscope of adverse effects on human health, including cardiac biology, and especially in vulnerable subjects, such as those with an inherited, pro-atherosclerotic milieu (11). The time has probably come to start protecting the environment for protecting ourselves, especially the most vulnerable of us.

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Footnote

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