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GENETIC PREDISPOSITION TO ISCHEMIC HEART DISEASE

Paolo Severino*, Andrea D'Amato, Mariateresa Pucci, Lucrezia Netti, Massimo Mancone, Francesco Fedele
Department of Cardiovascular, Respiratory, Nephrology, Anesthesiology and Geriatric Sciences. Sapienza University of Rome

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Abstract
Among cardiovascular disease, ischemic heart disease (IHD) is the most frequent cause of mortality all over the world[1]. However, as well known, CAD and IHD are not always synonymous. In fact, there are other pathophysiological mechanisms which have a role in IHD development[2,3]. Possible underlying mechanisms include coronary microvascular dysfunction (CMD), coronary spasm and coronary dissection.

Introduction

Among cardiovascular disease, ischemic heart disease (IHD) is the most frequent cause of mortality all over the world[1]. Conventionally, IHD is determined by the presence of coronary artery disease (CAD), defined as a condition characterized by the presence in the coronary tree of an atherosclerotic plaque which reduce more than 50% the artery diameter. However, as well known, CAD and IHD are not always synonymous. In fact, there are other pathophysiological mechanisms which have a role in IHD development[2,3]. Possible underlying mechanisms include coronary microvascular dysfunction (CMD), coronary spasm and coronary dissection. Among them, CMD is a condition caused by the impairing of endothelium-dependent, or independent, vasodilation response, that is able to provoke myocardial ischemia and infarction, independently from the presence of CAD[2–4]. In fact, results from the WISE (Women's Ischemia Syndrome Evaluation) suggest that nearly 30% of patients presenting with symptoms/signs of IHD have CMD and not CAD[5]. There are different cardiovascular risk factors which play a main role in IHD pathogenesis[6]. However, in the last decades several evidences showed the crucial role of genetic susceptibility in IHD pathogenesis[7]. Genetic susceptibility may act both independently by conventional risk factors and in association with them in the determinism of CAD and/or microvascular dysfunction[7,8] and, therefore, IHD. The genetic susceptibility has a primary role in the etiology of the IHD[7]. Several genome wide association studies (GWAS) have allowed to identify numerous single nucleotide polymorphisms (SNPs) related to IHD[8]. SNP is a variation of a single nucleotide in the DNA sequence of an individual, compared to the normal population, and present in more than 1% of population. This variation could be due to a delection, an insertion or a substitution and it may involve both coding and non-coding regions of DNA. The identification of SNPs related to IHD may be important for setting up a genetic risk score which may provide additional information to estimate the global cardiovascular risk of patients when the genetic one is integrated with the conventional risk score[9]. The SNPs predisposing to CAD affect several regions of the DNA involved in the determinism of the diabetes mellitus, the arterial hypertension, the dyslipidemia and the atherosclerosis[10]. The SNPs predisposing to the microvascular dysfunction affect genes coding for proteins involved in the regulation of coronary blood flow, as endothelial nitric oxide synthase (eNOS) and ion channels[3]. The aim of this review, through the latest data obtained from the international literature, about the genes and the related SNPs predisposing both to the alterations of epicardial vessel and/or to the microvascular dysfunction.

Cardiovascular risk factors

Seventy years ago, the Framingham Heart Study enrolled its first participant. This study has provided remarkable insights into the epidemiology of cardiovascular disease and its risk factors. Nowadays, it is well known that several are the cardiovascular risk factors acting in IHD pathogenesis[6]. Some are modifiable as systemic arterial

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hypertension, diabetes mellitus, blood lipid levels, alcohol consumption, body weight, and lack of physical activity[11] ; others are not modifiable, as male sex, age and genetic susceptibility[6]. The main IHD risk factors coincide with atherosclerosis and endothelial dysfunction risk factors and, apart from age, familiarity and genetic alterations, they are modifiable conditions predisposing to the development of the atherosclerotic plaques, that reduce the coronary lumen and lead to ischemic events. Therefore, risk factors contribute both to the loss of endothelial function[12] and to the chronic inflammation[13]. Smoking, arterial hypertension, dyslipidemia, obesity and diabetes mellitus are the primary and most significant risk factors co-working to create a pathological background favoring the aggravation of coronary stenosis by the atherosclerotic plaque increase. In fact, these conditions impair the normal endothelial function, which progressively lose the ability to maintain vascular homeostasis, modulating vascular tone and blood flow, cell adhesion, immune response and vascular remodeling[14]. Through the interconnection and interweaving of multiple mechanisms, got by different ways as raising ROS production, weakening antioxidant defense and enzymes, reducing eNOS and prostacyclin synthase activity, increasing endotelin-1 levels, cytokines and platelet adhesion and aggregation, augmenting free fatty acids (FFA), advanced glycation products (AGEs) and oxyLDL levels[15–17], smoking, arterial hypertension, dyslipidemia, and diabetes mellitus interfere with the physiological role and function of coronary artery endothelium, causing reduced bioavailability of NO and vasodilation, stimulated vasoconstriction, accentuated endothelial permeability with the creation of a pro-thrombotic surface, boosted oxidative stress and amplified inflammatory climate that predispose to atherogenic phenomena[18–24]. All these pathological conditions put the coronary arteries in difficulty in guaranteeing an adequate supply of blood, and therefore of oxygen, to the myocardium, predisposing to the genesis of IHD in one of its different clinical forms.
Although globally exists a huge effort for early diagnosis and prevention as life-style and/or pharmacological treatment of these main cardiovascular risk factors, in the last decades, incidence of IHD does not significantly decrease. A growing body of evidences showed that genetic factors may have a decisive role in IHD pathogenesis[7], independently from presence of risk factors or in association with them in the determinism of CAD and/or microvascular dysfunction[7,8].

SNPs and diabetes mellitus

The presence of SNPs in genes related to the regulation of glucose metabolism may_influence the risk of IHD. Genetic factors play a significant role mostly in the susceptibility to the type 2 of diabetes mellitus rather than the type 1. The growth arrest-specific gene 6 (Gas6) is mapped on chromosome 13q34 and encodes for the plasmatic, vitamin k-dependent protein GAS6, which interacts with tyrosine kinase receptors of TAM family[25]. This pathway is involved in several functions such as the regulation of cell migration and cell surviving and death. Kazakova et al. have demonstrated that the presence of allele T in the polymorphism rs8191974 of Gas6 predispose to type 2 of diabetes mellitus and is related to cardiovascular complications, altering beta cells function[25]. The adapter-related protein complex 3 subunit sigma-2 gene is mapped on 16q26 and encodes for a transport protein[25]. The same study by Kazakova et al. demonstrated that the rs2028299 polymorphism of this gene is related to diabetes mellitus[25]. Indeed, this causes the insulin receptor intracellular distribution alteration and micro-RNA expression alteration which is related to a reduction of insulin secretion[25]. T-caderine (CDH13) is an adiponectin receptor expressed by endothelial and smooth muscle cells and it is involved in insulin secretion and adiponectin action regulation[26]. Li et al. evidenced that rs12596316 (AG), rs11646213, rs3865188, rs12444338, rs12051272 and rs7195409 polymorphism represents hypertension and metabolic syndrome risk factors, for differnt populations[26]. PRKAA2 is a gene which encodes for alfa2 subunit of AMPK, a protein involved in insulin sensitivity and lipid metabolism regulation[27]. According to a study by Li et al. rs10789038 (GA and GG) and rs2796498 polymorphisms of this gene reduce the protein activity, increasing the risk to develop diabetes mellitus. Rs2796498 (GA and AA) polymorphism has a protective role against diabetes mellitus development[27]. It has been proposed that chronic inflammation state might be associated with cardiovascular risk factors and IHD[28]. The SNPs for genes encoding for cytokines and their receptors genes predispose to metabolic syndrome and its cardiovascular complications. Indeed, an increase of cytokines and their receptors activity cause chronic inflammation[28]. Norde at al. demonstrated that the presence of G allele of rs1800795 polymorphism of interleukin 6 gene (IL-6) is associated with high IL-6 plasmatic values[29]. This condition is involved in the metabolic syndrome and in cardiovascular complications. Rs16944 polymorphism of interleukin 1B (IL-1B) gene is related to an increased risk of metabolic syndrome and hypertension[29]. Some authors evidenced an increased incidence of the type 2 of diabetes mellitus in people who has the T allele of rs1143634 polymorphism of IL-1B gene[29]. Rs1800196 polymorphism of IL-10 gene is associated with a high cardiovascular

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risk, while -819T/C polymorphism is related to the type 2 of diabetes mellitus[30]. PSD3 gene is situated on chromosome 8p22 and is expressed in several types of tissues, among which heart and pancreas[31]. According to a study by Gong et al, this gene is a potential onco-suppressor which plays an important role in the immune response[31]. There are six polymorphisms for this gene which are related to the development of the diabetes mellitus: rs12156368, rs6983992, rs7843239, rs17127410, rs6993670, rs7009615[31]. AdipoQ gene encodes for the adiponectin, a hormone that is specifically synthesized by the adipose tissue. Momin at al. have identified two SNPs, +45T/G and +276G/T which are respectively situated in the second exon and the first intron of the same gene and are related to the development of type 2 of diabetes mellitus and IHD[32]. However, only +45T/G is associated with the insulin resistance[32]. The presence of both polymorphic variants has a stronger effect on the onset of type 2 diabetes mellitus than the presence of only one variant[32]. Klarin et al. have demonstrated the relationship among the obesity, the insulin resistance and the coronary artery disease and the polymorphism rs11057401 of the gene CCDC92[33]. TCF7L2 encodes for a transcription factor involved in the regulation of the pathway of WNT and allelic variants on this gene may be associated with the dysfunction of beta cells and a lower secretion of insulin[34]. According to Haddad et al. the polymorphism rs7903146 of the gene TCF7L2 is the main allelic variant associated with the type 2 of diabetes mellitus in several populations[34]. Among the SNPs of the region of PSMD2 gene, rs2178403 represents the meaningful one involved in the susceptibility to the type 2 of diabetes mellitus[34]. It affects the gene EIF4GI which encodes for an enzymatic complex involved in the processing of pro-insulin[34]. A study by Wang et al. have showed the relationship among the presence of the rs5742612 and rs2288377 SNPs of the gene encoding for the insulin growth factor 1 (IGF1) and the alteration of the insulin sensitivity and secretion [35]. The TT genotype shows a greater insulin sensitivity and a lower insulin secretion than C and A alleles of the first and second polymorphism which show a lower insulin sensitivity and a greater insulin secretion[35].

SNPs and dyslipidemia

Hyperlipidaemia and hypertriglyceridemia represent important risk factors for IHD. PCSK9 is a protein that is encoded by the homonymous gene on 1p32. It links the LDL receptor and allows its degradation. Therefore, PCSK9 is involved in the regulation of cholesterol metabolism. The SNPs for this gene which are related to high plasmatic level of LDL are rs12067569 and rs505151 (named also E670G)[36]. Olza et al. have confirmed the association among four SNPs for the gene FTO and dyslipidemia both in adult and in child. These SNPs are situated in the intron 1 of FTO gene and are rs9928094, rs9939609, rs930333 and rs9935401[37]. Hubaceck et al. have studied the polymorphic variants of SORT1 (rs646776), APOE (rs4420638), CLIP2 (rs16996148), APOB (rs693) and LDL-R (rs6511720) genes both in male and in female and they have confirmed their association with plasmatic levels of LDL[38]. Ripatti et al. have studied the relationship between SNPs of genes normally associated with some types of monogenic transmission dyslipidemia to clarify the pathogenesis of combined family dyslipidemia, characterized by high plasmatic levels of triglycerides and total cholesterol and associated with IHD. The greatest contribution comes from the APOE, LIPC genes as regards LDL and APOA1, APOC3, APOA4, APOA5 as regards triglycerides. On the contrary the 75G/A polymorphism of APOA1 has a protective role as regards CAD[39]. Guay et al. have demonstrated that the polymorphism c.-20G>A of the locus 19q13.42 may be responsible of the reduction of HDL plasmatic levels through the metilation of DNA of TNNT1 gene in male with or without family hypercholesterolemia. The same authors have also demonstrated the association between plasmatic levels of HDL and metilation of DNA of the same gene, independently from the presence of the polymorphism; finally, both the genetic and epigenetic alteration of the same gene have the same impact on the HDL plasmatic levels and therefore on CAD risk[40]. Nuclear receptor co-activator 3 (NCOA3) has a very important role in the regulation of adipogenesis, checking the differentiation and development of adipocytes. Yu et al. have demonstrated a strong association between the polymorphism rs2425955 of the NCOA3 gene and hypertriglyceridemia[41]. Lv et al. have discovered two new SNPs of two genes related to body mass index (BMI) and CAD. They are rs653178 in the intronic region of ATXN2 and rs794356 of HIP1[42]. Among the multiple mechanisms underlying the generation and progression of atherosclerotic plaque by creating a state of endothelial dysfunction, mostly in the early phase of the process, there is the contribution of increased oxidized-low density lipoproteins (oxyLDLs)[43]. They contribute to the overproduction of ROS, which act both altering the eNOS functionality and amplifying the expression of the inducible pro-inflammatory iNOS and the caspase 3, a condition associated with the increase of endothelial cells apoptosis[43]. In the pathogenetic process, among the various factors, characteristically emerged the role of lectin-like oxidized LDL (LOX-1), a scavenger receptor expressed on the surface of the endothelial cells, that selectively internalizes the oxyLDLs, as leading actor

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of a phenomenon in which it induces the attenuation of the endothelial protective autophagic response to oxidative insults, promoting cell apoptosis[43]. LOX-1 is greatly expressed in atherosclerotic plaques and therefore the overexpression of this receptor, injuring the endothelial function, amplifies the pathological process of the plaque formation in the atherosclerosis background[44]. Skarpengland et al. observed elevated soluble lectin-like oxidized low-density lipoprotein receptor-1 (sLOX-1) levels in patients with carotid plaque affected by transient ischemic attack or ischemic stroke, independently from the cause of the cerebral event[45]. In patients affected by extreme obesity, a SNP for the ARPC3 Gene Promoter was associated with hypertriglyceridemia[46]. Moreover, among different ethnicities Lysosomal Acid Lipase A (LIPA), specific polymorphisms have been associated with susceptibility to premature coronary artery disease[47].

SNPs and arterial hypertension

Systemic arterial hypertension is one of the most important risk factor both for CAD and CMD. PHATCR1 gene modulates endothelin-1 gene expression and its polymorphism rs9349379 is linked with arterial hypertension and CAD[48]. Wang et al. have demonstrated that the A allele of rs2779249 and rs2297518 polymorphisms of the nitric oxide inducible synthetase (iNOS) gene predisposes to arterial hypertension through an overexpression of this enzyme which consequently causes an increase of nitric oxide plasmatic levels which compromises cell breathing causing endothelial damage[49]. C4BPA encodes for the alfa chain of C4BP, an acute phase protein, whose plasmatic levels are related to essential arterial hypertension and myocardial infarction[50]. As evidenced by the study by Liu et al. the rs73079108 polymorphism is related to an increased expression of this gene and risk to develop myocardial infraction and arterial hypertension, mostly in obese women[50]. However, the presence of A allele in the same polymorphism may be a protective factor for the development of the previously defined conditions[50]. Yamada et al. showed that the rs12229654 polymorphism mapped on 12q24.1 is related to systolic and diastolic pressure values[51]. Through this association this locus may be important in predisposition to arterial hypertension and metabolic syndrome[51]. According to the same study, other five polymorphisms in other four loci may be related to arterial systolic and diastolic pressure values and therefore to arterial hypertension[51]. They are rs3782886 of BRAP gene, rs671 od ALDH2 gene, rs2074356 and rs11066280 of HECTD4 gene and rs11066015 of ACAD10 gene[51]. Bayoglu et al. studied the relationship between arterial hypertension and the locus 9p21.3[52]. In this region the non-coding RNA CDKN2B-AS1 which is involved in epigenetic regulation of other genic loci is mapped[52]. For this reason the rs2383207, rs1333049, rs10757274, rs10757278 SNPs of this region may be associated with arterial essential hypertension[52]. The AA genotype of rs10757274 e rs2383207 and GG genotype of rs1333049 are related to high arterial pressure values despite the anti-hypertensive therapy[52]. Li et al. pointed out the association between the CYP17A1 gene, encoding for homonymous cytochrome, and both diastolic and systolic pressure values[53]. Two polymorphisms for this gene, rs11191548 (A>G) e rs4919687 (C>T), are mainly associated to hypertension[53]. Zhang et al. focused their attention on the relationship between another member of cytochrome family, CYP4A11, and arterial pressure values[54]. For this reason C and G alleles of rs1126742 and rs389001 polymorphisms are strongly associated with the risk of arterial hypertension[54]. This study underlines also that among the people with this genetic background for CYP4A11, smokers have a greater risk to develop essential hypertension than non-smokers[54]. Polonikov et al. also studied the family of cytochrome P-450 and they showed the strong association between the rs7909236 polymorphism of CYP2C8 gene and the risk to develop essential hypertension[55]. Furthermore, the association of the TT genotype of this polymorphism with GG genotype of rs4244285 polymorphism of CYP2C19 gene is associated to a higher risk to develop essential hypertension than the presence of the only last SNP[55]. Al Refai et al. demonstrated the association between the T allele of G894T polymorphism of eNOS gene and both arterial hypertension and CAD mostly in older and dyslipidemic patients[56]. Xia et al. identified two polymorphisms of the adrenergic receptor gene. They are ADRA2B (D/I) and ADRB1 (Ser49Arg) and influence both arterial pressure values and lipid metabolism, predisposing to IHD[57]. A recent study of genome wide association has allowed to identify nine new genic loci which are able to influence arterial pressure values[58]. They are TARID/TCF21 (rs76987554), FRMD3 (rs115795127), LLPH, TMBIM4 (rs113866309), GPR20, CDH17, TCF21, ULK4 ed EVX1/HOXA[58]. Scurrah et al. studied the association between genes which encodes for several proteins belonging to renin-angiotensin-aldosterone system and arterial pressure[59]. They demonstrated that rs8075924 and rs4277404 polymorphisms of angiotensin converter enzyme gene (ACE) and rs12721297 polymorphism of angiotensin receptor 1 gene (AGRT1) are associated to arterial pressure values in male gender[59]. Two SNPs, rs11658531 and rs12451328 of ACE gene are related to arterial pressure values and therefore to hypertension,

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respectively, in male and female gender[59]. The CG genotype of -174G/C of IL-6 gene and the allele A in C-1260A of CYP27B1 are related to the early onset and rapid aggravation of hypertension complications[60]. Moreover, PDE3A, PRDM6, IGFBP3, and KCNK3 genes modulate vascular smooth muscle cells[61]. In particular, PDE3A is phosphodiesterase which acts in cyclic GMP metabolism[62], while KCNK3 has been related to pulmonary hypertension[63].

SNPs and atherosclerosis

The research of the SNPs predisposing to atherosclerosis underlines the importance of the genetic susceptibility as a fundamental factor as regards not only the pathogenesis but also the evolution of this disease towards IHD. Myeloperoxidase (MPO) promotes the inflammatory response and it has an important role in the pathogenesis of atherosclerosis[64]. Wang et al demonstrated that the 463G/A polymorphism of MPO gene predisposes to atherosclerosis and therefore CAD in Asian population[64]. ERCC1 encodes for a protein involved in DNA reparation in several diseases among which atherosclerosis[65]. Zhang et al. evidenced that the presence of T allele of rs11615 polymorphism of ERCC1 gene is associated to a greater risk to develop a severe type of CAD[65]. Larsson et al. studied the association of allelic variants of genes involved in plasmatic calcium levels regulation and CAD and myocardial infarction[66]. Their study showed that CYP24A1 (rs1570669), DGKH/KIAA0564 (rs7336933), CASR (rs1801725), GAT3 (rs10491003), DGKD (rs1550532), CARS (rs7481584) are associated to higher plasmatic calcium levels and to a higher risk to develop CAD[66]. Toutouzas et al. demonstrated through coronary angiography, that patients with diagnosis of CAD (stable/unstable angina), who had -174C allele of IL-6 gene, showed a faster evolution of CAD in a period of four years[67]. Paquette et al. studied 9p21.3 locus in patients with family hypercholesterolemia[68]. This genic locus is mostly associated to the risk to develop atherosclerosis and its complications in normal population[68]. In patients with family hypercholesterolemia, the rs1333047 SNP increases further the risk to develop atherosclerosis[68]. Ansari et al. demonstrated that several polymorphisms in different genes predispose to an early form of ischemic heart disease because they lead to a variation of cytokines plasmatic levels, mostly IL-10, IL-18 and TNF-alfa[69]. APOE (rs7412 and rs429358), 9p21 (rs10757274), CXCL12 (rs1746048), SORT1 (rs646776), MIA3 (rs17465637) are associated to CAD and in particular APOE (rs429358) is mainly associated to cytokines plasmatic levels alterations[69]. Moreover, the −174 C allele of the IL-6 gene increases the risk for progression of coronary plaques in patients with established coronary artery disease[67]. Also, patients with the Cox-2 GG single-nucleotide polymorphism show a increased risk to develop CAD while the Cox-2 (−765G>C) polymorphism correlates with reduced interleukin-6 levels[70].In a study concerning European, Asiatic and Afro-American populations Howson et al. identified fifteen new genomic regions involved in CAD, within them there are several genes involved in inflammatory response, coagulation and smooth muscle cells differentiation regulation[71]. The genes are: DDX59-CAMSAP2, ARHGAP26, PCNX3, LMOD1, ATP1B1, TNS1, PARP12, SERPINH1, SCARB1, DHX38, PECAM1, GOSR2, OAZ2, RBPMS2, C12orf43-HNF1A, PROCR[71]. The study by Masud et al. evidenced the association among the rs1801133 (C>T) of MTHFR and rs1805087 of MTR and homocysteine plasmatic levels which are related to the risk to develop atherosclerosis[72]. Li et al. studied the relationship among the polymorphisms of atrial natriuretic peptide gene and CAD observing their different effect on male and female gender[73]. The AA genotype of rs198389 polymorphism of NPPB gene which encodes for natriuretic peptide B predisposes only female gender to a higher risk to develop both CAD and plaque breakage[73]. Through a meta-analysis study Webb et al. identified six new loci related to CAD and several of these are pleiotropic[74]. The six new loci are 16q13 (CETP), 12q13 (LRP1), 2q37 (KCNJ13- GIGYF2), 12q24 (SCARB1), 11p15 (MRV11-CTR9), 6p21 (C2)[74]. In atherosclerotic plaques CB2 gene (CNR2) is overexpressed, compared with normal arteries. It is a marker of inflammation, and similar CNR2 levels are expressed in both stable and vulnerable plaques[75]. Braenne et al. identified several genes which undergo to an inhibition or down-regulation consequently to the administration of anti-inflammatory drugs Coxib whose assumption is related to an increase of cardiovascular risk[76]. In this way they identified new loci related to CAD. These loci are MMP9 (rs7270354), CACNA1E (rs556321), BCAR1 (rs4888383), VEGFA (rs6905288)[76].

SNPs and coronary microvascular dysfunction

Lower bio-availability of nitric oxide is associated to a reduction of endothelia-dependent vasodilation but also to an increase of shear stress in the epicardial district, which predisposes to the development and evolution of atherosclerotic plaque[3]. Ekmekci et al. demonstrated that the presence of “a” allele of the polymorphism of “4 a/b”

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intron of eNOS gene is associated to an increase of eNOS expression, but to a reduction of its function with the following reduction of nitric oxide levels, compared to the wild-type "b" allele[77]. This condition contributes to determine slower coronary blood flow which is an angiographic phenomenon, expression of microvascular dysfunction[77]. Also, the T-786C polymorphism of eNOS predisposes to a slower coronary blood flow. We reported[3] that the rs1799983 polymorphism (GT) of exon 7 (Glu298Asp, CAG-GAT) of eNOS/NOS3 gene is an independent risk factor of microvascular dysfunction. The vascular endothelial growth factor A and its receptor are involved in angiogenesis and layering of vessels' wall and a reduction of their function due to the presence of SNPs in respective genes may be involved in microvascular dysfunction[78]. Li et al. highlighted that the rs3025039 polymorphism may predispose to microvascular dysfunction both male and female gender, while the rs3025028 polymorphism only male gender[79]. The rs2010963 (CG) polymorphism is associated to IHD, in absence of conventional cardiovascular risk factors[80]. Another study demonstrated that, beyond the rs3025039 polymorphism, other two polymorphisms of VEGFA, rs699947 and rs1570360 and the rs1870377 rs2305948 and rs7667298 polymorphisms of the receptor 2 of VEGFA (VEGFR2) increase the risk to develop IHD[81]. The association of some VEGFA and VEGFR2 polymorphisms, for example rs1870377 (TA) and rs699947 (CA/AA) increases further IHD risk[81]. The rs6999647, rs2305948 and rs1870377 SNPs are independent risk factors of IHD and they may be useful as genetic markers to evaluate the predisposition to IHD[80]. On 9p21.3 chromosome, there is a genic locus which maps for CDKN2BAS, an antisense, non-coding RNA[82]. CDKN2BAS is normally present inside endothelial and smooth muscle cells of coronary vessels[82]. Five polymorphisms for this gene, are identified by Schaefer at al. They are rs10757274, rs2383206, rs1004638, rs2383207 and rs1333049 and determine a deficit of CDKN2BAS, increasing inflammatory response and endothelial cells death predisposing to atherogenesis the patients who already had microvascular dysfunction[82]. ABCG2 gene encodes for ATP-binding cassette, a sterol transporter, expressed on endothelial cells of coronary arteries[83]. The Val12Met (rs2231137) polymorphism is associated to endothelial dysfunction and to an increase of cardiovascular risk both in white and black patients[83]. The cytochrome P450 2C19 (CYP2C19) is an enzyme expressed by endothelial cells and responsible of epoxyeicosatrienoic acids (EETs) production[84]. These are molecules with both strong anti-inflammatory power because they are able to inhibit the transcription factor nf-Kb, and vasodilator activity because they allow the opening of calcium-dependent potassium channels[55,84]. The activity of CYP2C19 is reduced in slow metabolizers, subjects which have a double allelic loss on the relative gene, in contrast with normal ones, who have only a single or none allelic loss[84]. The slow metabolizer, producing a reduced amount of EETs, is predisposed, regardless of the conventional risk factors, to develop microvascular dysfunction due to chronic inflammation[84]. A meta-analysis study by Ikram et al. identified four new polymorphisms on four genetic loci. They are 19q13 (rs2287921), 6q24 (rs2257717), 12q24 (rs10774625) and 5q14 (rs17421627) and they are associated to retinic microvascular venules diameter alterations, which are related also with coronary microvascular dysfunction[85]. The rs2287921 polymorphism of RASIP1 gene represents the mainly associated polymorphism with retinic veins diameter[85]. RASIP1 belongs to RAS family and it's expressed in endothelial cells where it checks cellular migration[86]. The rs10774625 polymoprhism of 12q24 locus is significantly associated to coronary microvascular dysfunction. In the same genic region there are other genes among which PTPN11, ATXN2 and SH2B3 which are related to retinic venular diameter[85,86]. A study of genome wide association allows to identify two SNPs related to IHD, which are rs11065987 of ATXN2 and rs11066301 of PTPN11, and one SNP (rs3184504 in SH2B3) related to type 2 of diabetes mellitus, a condition in which microvascular dysfunction is a frequent complication[85]. The rs17421627 polymorphism on 5q14 is located in an intragenic region which modulates the transcription factor myocyte enhancer factor 2 (MEF2C) expression, which is important for cardiogenesis and vessel's integrity[85]. The study by Dou et al. have demonstrated that microvascular dysfunction is more frequent in older and obese patients than younger ones[87]. In these patients the age and the exposition to risk factors determine the reduction of caveolin-1 expression and the following increased expression of ADAM17 in endothelial cells of adipose tissue vessels[87,88]. This is the main mechanism responsible of coronary microvascular dysfunction in these patients[89]. ADAM17 modules TNF soluble fraction levels[88]. An increasing of ADAM17 biological activity is associated with higher plasmatic TNF values which contributes to support a chronic inflammatory state which is involved in coronary microvascular dysfunction and CAD[87]. Among several NADPH isoforms, NOX1 is that one mainly expressed by coronary microvascular endothelial and smooth muscle cells. NOX1 is the main source of superoxide anions both in physiological and in pathological conditions[90,91]. In patients with metabolic syndrome, NOX1 amplifies endothelial damage caused by metabolic alterations[91]. It is overexpressed in microcirculation vessels endothelial cell lines, in presence of glucose high levels and contributes to

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determinate early endothelial damage before the developing of hypertension and the consequent complications[90]. A study by Thompson et al. have demonstrated that the administration of an inhibitor of NOX1/4 in guinea pigs improves endothelial-dependent vasodilation[92] through the normalization of superoxide anions values which determines the reactivation of nitric oxide production[90]. In the future, the selective inhibition of NOX1 may be used to contrast microvascular dysfunction, in patients with metabolic syndrome[90]. In patients with hypertrophic cardiomyopathy, coronary microvascular dysfunction represents a condition related to a deadly prognosis[93]. Sarcomeric myofilaments proteins mutations are associated with a type of hypertrophic cardiomyopathy with faster evolution[94]. Causing microvascular dysfunction these mutations are responsible of vessels and myocardial fibrosis and remodelling[95]. According to Olivotto et al., among these mutations the most frequently observed are in MYBPC3 and MYH7, followed by the mutations of MYL2, TNNT2, TNNT3 and TPM1[93]. Paroxonasi 1 (PON1) protects LDL by oxidative damage and therefore endothelium by oxidized LDL[96]. As evidenced by Mashiba et al. A632G polymorphism of PON1 reduces PON1 biological activity, predisposing to vasospasm both the genders and to microvascular angina only the female gender[97]. Erythroid nuclear derived factor 2 (NRF2) is a transcription factor which stimulates cellular antioxidant enzymatic complexes genes[98]. A study by Priestly et al. have demonstrated that the NRF2 gene delection has an important role in oxidative stress damage, in endothelial dysfunction and in microvascular rarefication, in guinea pigs[99]. Hypoxia induced factor 1 (HIF-1) regulates the expression of several genes as that one which encodes for eme-oxygenase (HO-1)[100]. HO-1 regulates chemokines expression from microvascular endothelial cells in ischemic-reperfusion conditions both in vivo and in vitro[100]. Dimetiloxalilgycine (DMOG) administration, a prolil-hydrolase inhibitor, determines an increasing expression of HIF-1 and of HO-1, defending the myocardium by ischemic-reperfusion damage[100]. The Kv1.3 subunit of voltage dependent potassium channel modulates microvascular vessels tone mediating the relationship between coronary blood flow and myocardial metabolism[101]. The activation of this channel is caused by hydrogen peroxide (H2O2)[101]. The exposition of isolated vessels from guinea pigs treated with correolide (inhibitor of potassium channels) or in which the Kv 1.3 gene was deleted is not associated with activation of these channels and therefore vasodilatatory response is compromised[101]. The loss of function of these potassium channel subunits has a main role in microvascular dysfunction and CAD[102]. Produced within a certain range the H2O2 modulates coronary blood flow while an excess of its production is associated with endothelial damage[103]. As regards, also TRPV1 channel mediates H2O2 dependent vasodilatation[103]. This condition is reduced both in TRPV1 knock out mice and in diabetic mice in which the excessive ROS production causes microvascular dysfunction[103]. As observed in pigs with metabolic syndrome, reduced expression of calcium-dependent potassium channels on smooth muscle cells of microvasculature is associated with an increased vasoconstrictor activity mediated by type L calcium channels[104].

There are gender differences on the impact of several polymorphisms in microvascular dysfunction and cardiovascular damage. Rs4855559 and rs7630352 polymorphisms of MYH15 gene which encodes for the 15 heavy chain of myosine, are associated with the coronary blood flow (CFR) reduction[79]. The mechanisms with which they cause microvascular dysfunction are unknown too[83]. Vascular tone upregulation and inflammation contribute to microvessel stiffness in males. In particular, single-nucleotide polymorphisms of MYH15, involved in the development of tonic force in vascular smooth muscle cells, VEGFA, which is implicated in cell migration, proliferation, and angiogenic potential and NT5E involved in microvessel calcification were associated with microvascular dysfunction in men[77,105]. Coronary microcirculation dysfunction can also occur in cardiac hypertrophy, which can be related to the expression of Kvβ1.1, especially in women. In animal models, Kvβ1 KO female mice have a higher expression of myosin heavy chain α in myocytes. This may cause electrical and structural remodeling with the development of cardiac microvessel disease[106]. Moreover, the specific CYP2C19 poor metabolizer may play the role of risk factor for coronary microvascular dysfunction through the inflammation, only in the female population[107]. NT5E gene encodes for CD73, a protein involved in the transformation of AMP in adenosine[79]. Its polymorphism rs6922 is responsible of a deficit of NT5E which causes a reduction of extracellular adenosine levels supporting arterial wall calcification and therefore CFR reduction, mostly in male gender[79]. This SNP is an independent risk factor for microvascular dysfunction and CAD[79].

Conclusions

Pathophysiology of IHD is more complex and multifaceted that a single, simplistic, cause-effect event. In fact, both clinical, angiographic, and autoptic findings suggest a complex, not fully known, pathophysiology for IHD.

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Although prevention, early diagnosis and treatment of the main cardiovascular risk factors, in the last decades, incidence of IHD does not significantly decrease. Probably, this is due to genetic factors play a significant role in IHD pathogenesis, independently from presence of risk factors or in association with them in the determinism of CAD and/or microvascular dysfunction. In the last decades, several observations on the correlation of genetic profile and IHD susceptibility have been made. Basic and clinical researches proposed different SNPs encoding for mechanisms involved in CAD, CMD or risk factors for them. A few of them may remain speculative; others have functional and molecular evidences. In any case, this growing trend towards genetic aspects represents a modern piece in the huge puzzle of the complex pathophysiology of IHD.

Conflict of interest

Authors have no conflict of interest to declare..

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