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REVIEW ARTICLE

Sortilin and the risk of cardiovascular disease☆

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Abstract Plasma low-density lipoprotein cholesterol (LDL-C) levels are a key determinant of the risk of cardiovascular disease, which is why many studies have attempted to elucidate the pathways that regulate its metabolism. Novel latest-generation sequencing techniques have identified a strong association between the 1p13 locus and the risk of cardiovascular disease caused by changes in plasma LDL-C levels. As expected for a complex phenotype, the effects of variation in this locus are only moderate. Even so, knowledge of the association is of major importance, since it has unveiled a new metabolic pathway regulating plasma cholesterol levels. Crucial to this discovery was the work of three independent teams seeking to clarify the biological basis of this association, who succeeded in proving that *SORT1*, encoding sortilin, was the gene in the 1p13 locus involved in LDL metabolism. *SORT1* was the first gene identified as determining plasma LDL levels to be mechanistically evaluated and, although the three teams used different, though appropriate, experimental methods, their results were in some ways contradictory. Here we review all the experiments that led to the identification of the new pathway connecting sortilin with plasma LDL levels and risk of myocardial infarction. The regulatory mechanism underlying this association remains unclear, but its discovery has paved the way for considering previously unsuspected therapeutic targets and approaches.

PALAVRAS-CHAVE
Genome wide association studies;
Doença das artérias coronárias;

Sortilina e risco de doença cardiovascular

Resumo O nível plasmático de c-LDL constitui um determinante chave para o risco de doença cardiovascular, razão pela qual muitos estudos têm procurado elucidar as vias que regulam o seu metabolismo. As novas técnicas de sequenciação de última geração permitiram identificar

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um forte sinal de associação entre o *locus* 1p13 e o risco de doença cardiovascular causada por alteração dos níveis de LDL no plasma. Como seria de esperar para um fenótipo complexo, os efeitos da variação nesse *locus* são apenas moderados, ainda assim, o conhecimento da associação foi de grande importância uma vez que conduziu à descoberta de uma nova via metabólica reguladora dos níveis de colesterol no plasma. Para tal, foram fundamentais os trabalhos efetuados por três equipas independentes, que ao procurarem esclarecer as bases biológicas da associação em causa conseguiram provar que o gene *SORT1*, codificador da sortilina, era o gene do *locus* 1p13 implicado no metabolismo das LDL. *SORT1* foi o primeiro dos genes identificados como determinantes dos níveis plasmáticos de LDL a ser alvo de avaliação mecanística e embora cada uma das equipas recorresse a metodologias experimentais diferentes, mas igualmente apropriadas face à questão em investigação, os resultados que obtiveram foram contraditórios em alguns aspetos. Neste trabalho, revemos o caminho percorrido até à descoberta da nova via que relaciona a sortilina com os níveis plasmáticos de LDL e com o risco de enfarte do miocárdio. Ainda por esclarecer permanece o mecanismo regulador dessa ligação, mas a sua descoberta sugere novos alvos terapêuticos até há bem pouco tempo desconhecidos.

List of abbreviations

apo	apolipoprotein
C/EBP	CCAAT/enhancer binding protein
CAD	coronary artery disease
CVD	cerebrovascular disease
GLUT4	glucose transporter 4
GM2AP	GM2 activator protein
GWAS	genome-wide association studies
HDL	high-density lipoprotein
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein
LPL	lipoprotein lipase
MI	myocardial infarction
RAP	receptor-associated protein
SAP	sphingolipid activator protein
siRNA	short interfering RNA
SNP	single-nucleotide polymorphism
TC	total cholesterol
VLDL-C	very low-density lipoprotein cholesterol

Introduction

Cardiovascular disease is the leading cause of death in developed countries,[1] and is responsible for 32% of deaths recorded in Portugal, according to the National Institute of Statistics.[2] Coronary artery disease (CAD), in particular, represents a major clinical problem, accounting for one in five deaths in the US.[3,4] Multiple factors contribute to the development of CAD but it is well established that one of its key determinants is plasma LDL-C level. According to estimates by the WHO, about 9 million deaths/year and more than 75 million years of life lost/year are due to hypertension or hypercholesterolemia.[5] Overall, hypercholesterolemia is responsible for 18% of recorded events of cerebrovascular disease (CVD), mostly non-fatal events, and 56% of ischemic heart disease.[5] The data for Europe suggest that hypercholesterolemia may be responsible for up to 12% of disability-adjusted life years.[5] Given the size of these numbers, many attempts have been made to elucidate the pathways that regulate LDL metabolism. It is now known that, for small groups of individuals, high cholesterol levels may be of genetic origin. There is even a Mendelian disease associated with high blood cholesterol: familial hypercholesterolemia.[6] Most patients suffering from this condition present pathogenic mutations in the gene that codes for the LDL receptor (*LDLR*), but it has been reported that defects in the apolipoprotein (apo) B gene (*APOB*), or less commonly, in the proprotein convertase subtilisin/kexin type 9 (*PCSK9*) gene, may also be associated with this clinical phenotype.[6,7] Mutations in any of these genes lead to either loss (*LDLR* and *APOB*) or gain (*PCSK9*) of function of its associated protein and high cardiovascular risk.

However, there are few cases in which it is possible to relate a specific gene mutation to CVD. The pathogenesis of the major forms of CVD involves behavioral, environmental and genetic factors and the genetic component is known to be highly complex, resulting from the interaction of multiple genetic determinants.[8] There are, however, several polymorphisms in these and other genes involved in lipid metabolism that, even though presenting a smaller effect on the protein for which they code, may play a significant part in CVD risk (reviewed in [6]).

With the advent of new sequencing technologies, the search for a deeper understanding of these mechanisms, as well as the genetic basis of other risk factors, has gained new impetus; it has become possible to screen large populations for the genetic basis for complex diseases. Ultimately, such epidemiological studies may lead to a better understanding of etiological pathways and contribute to the development of new strategies for prevention and treatment.[9]

Recently, large-scale genome-wide association studies (GWAS) have made it possible to identify a novel set