Atherosclerosis 212 (2010) 16–29

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Review

Genetic and epigenetic mechanisms and their possible role in abdominal aortic aneurysm

Smriti M. Krishna[a], Anthony E. Dear[b], Paul E. Norman[c], Jonathan Golledge[a,*]

[a] Vascular Biology Unit, School of Medicine, James Cook University, Townsville, Queensland 4811, Australia
[b] ECRU Biotech Laboratory, Monash University, Melbourne, Australia
[c] School of Surgery, University of Western Australia, Fremantle Hospital, Fremantle, Western Australia 6959, Australia

ARTICLE INFO

Article history:
Received 2 December 2009
Received in revised form 29 January 2010
Accepted 4 February 2010
Available online 6 March 2010

Keywords:
Abdominal aortic aneurysm
Epigenetics
DNA methylation
Histone modifications
Epigenetic therapy

ABSTRACT

Abdominal aortic aneurysm (AAA) is a common disease associated with significant cardiovascular morbidity and mortality. The pathogenesis of AAA is poorly defined, making targeting of new therapies problematic. Current evidence favours an interaction of multiple environmental and genetic factors in the initiation and progression of AAA. Epigenetics is the term used to define the properties of the genome that are not explained by the primary sequence, but are due to the modifications of DNA and/or associated proteins. Previous research indicates the association of gene specific promoter DNA hyper-methylation and global DNA hypo-methylation with atherosclerosis. Evidence also suggests an important role for epigenetic processes such as histone acetylation in cardiovascular diseases including atherosclerosis and restenosis. Altered DNA methylation or histone acetylation occur in inflammation, cellular proliferation and remodelling processes and therefore maybe relevant to the pathology of AAA. Important risk factors for AAA, including cigarette smoking, older age, male gender and hypertension, have been linked with epigenetic effects and thus could act in this way to promote AAA. In this review, we discuss the potential role of epigenetic mechanisms in AAA. Since epigenetic alterations are to some extent reversible, further study of this area may identify new treatment targets for AAA.

Contents

* Corresponding author at: Vascular Biology Unit, Department of Surgery, School of Medicine, James Cook University, Townsville, Queensland 4811, Australia. Tel.: +61 7 4796 1417; fax: +61 7 4796 1401.
E-mail address: jonathan.golledge@jcu.edu.au (J. Golledge).

0021-9150/$ – see front matter © 2010 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.atherosclerosis.2010.02.008

1. Introduction

Gene expression patterns can be regulated at the genetic level by mutations or polymorphisms which affect the coding as well as non-coding sequence and also at the epigenetic level. Regulations of gene expression by epigenetic mechanisms are crucial determinants of cellular behaviour. Previous research suggests that environmental risk factors may promote complex diseases by stimulating a variety of epigenetic changes (reviewed in [1,2]). Epigenetic processes modulate the chromosomal organisation without altering the actual DNA sequence, and thereby contribute to the modulation of gene expression [1]. Epigenetic control of gene expression involves chromatin modification processes such as DNA methylation and several histone modifications including acetylation, methylation, phosphorylation and ubiquitinisation [1]. DNA methylation patterns are stably inherited upon mitosis in an adult cell, but deviations from the normal DNA methylation pattern may contribute to aging related diseases such as cancer and cardiovascular diseases [3]. The contribution of epigenetics to atherosclerosis has gained prominence recently due evidence that certain dietary components and smoking modulate DNA methylation in the arterial wall [4,5]. Since the methylation status of a gene or a change in chromatin structure is reversible, epigenetics has recently emerged as a potential molecular target for intervention [3].

Currently the contribution of epigenetic factors to the development of abdominal aortic aneurysm (AAA) has been little investigated. Histone acetylation levels have been demonstrated to vary in association with inflammation, proliferation and remodelling processes and thereby linked to atherosclerosis and restenosis [6]. In this review, we discuss the potential contribution of epigenetic mechanisms to AAA pathogenesis.

2. Abdominal aortic aneurysm

AAA (OMIM: 100070) is most commonly defined by an enlargement of the abdominal aorta to ≥30 mm, although other definitions also exist. AAA is associated with an increased risk of aortic rupture and also a high rate of other cardiovascular events, such as myocardial infarction, stroke and lower limb ischemia [7]. AAA affects approximately 5–7% of men and 1% of women over the age of 65, and is more common in smokers, subjects with dyslipidemia and hypertension [8,9].

At present the only accepted therapeutic option for AAA is repair of large AAAs by open or endovascular surgery [10,11]. Small AAAs (<50–55 mm depending on centre) are monitored by regular imaging until the AAA expands above the intervention size when surgery is considered. The "wait and watch" approach is currently adopted for small AAAs as randomized control trials such as the Aneurysm Detection and Management (ADAM) trial and the United Kingdom Small Aneurysm Trial (UKSAT) indicated that elective surgical repair did not improve the survival of patients with small AAAs [10,11]. Currently two large scale trials are being carried out to assess the value of endovascular repair of small AAAs. The European-based 17-site CAESAR (Comparison of surveillance *vs* Aortic Endografting for Small Aneurysm Repair) trial which has enrolled 740 patients with small AAAs (4.1–5.4 cm) has presented initial results suggesting no survival advantage of minimally invasive surgery for small AAAs [12]. The 70-site PIVOTAL (positive impact of endovascular options for treating aneurysm early) trial in the United States which has enrolled up to 1025 patients with small AAAs (4–5 cm), has currently not reported any results [12,13]. At present, if an AAA expands to have a maximum diameter >50–55 mm, surgery is usually undertaken depending on the patients operative risk [14]. Despite technical improvements in the surgical procedures and peri-operative care, AAA remains an important cause of death in many developed countries and the introduction of ultrasound screening of at risk groups in the USA, the UK and Europe is expected to lead to a large increase in the number of AAAs identified, particular small AAAs, over the next decade [15,16]. With an increase in the population >60 years in developed nations, an improved understanding of AAA pathogenesis would be expected to significantly advance current limited management options for this large group of patients.

It is believed that AAAs develops as a result of an imbalance between aortic extracellular matrix destructive and restorative processes. Histological examination of AAA biopsies shows that there is destruction of the normal lamellar architecture of the aorta, coupled with infiltration of inflammatory cells, including T/B lymphocytes, macrophages, neutrophils, mast cells and plasma cells [17]. Animal models suggest that AAA is a dynamic remodelling process, with neovascularisation, inflammatory cell infiltration, endothelial dysfunction, apoptosis and depletion of the vascular smooth muscle cells (VSMC) and destruction of the elastic media [18].

3. Genetic determinants of AAA

Up to 19% of patients report one or more first-degree relatives with an AAA suggesting a genetic predisposition for the condition [19,20]. In a nationwide survey in Sweden, it was observed that the relative risk of developing AAA for first-degree relatives to persons diagnosed with AAA was approximately doubled (OR = 1.9; 95% CI, 1.6–2.2, $p < 0.0001$) compared to persons with no family history [21]. Previous segregation studies using first degree relatives of AAA patients (91 probands) have suggested an autosomal recessive mode of inheritance for a predisposing gene [22].

A genome wide linkage analysis was carried out recently in 26 multiplex families with intracranial aneurysms (IA) from the Familial Intracranial Aneurysm study from North America, New Zealand, and Australia [23]. A number of subjects had both IA and aortic aneurysms (AAA cases = 91). The results support the concept of shared genetic risk among AAA and IA with maximum logarithm of odds (LOD) scores on chromosome 11 (144 cM; *LOD* = 3.0) and chromosome 6 (33 cM; *LOD* = 2.3) which was obtained using combined analysis of the various disease phenotypes. This indicates the contribution of shared risk factors to aneurysm susceptibility in various locations and also points to the fact that there could be common genes which acts as susceptibility factors.

Whole genome scan of 36 families (with at least two members with AAA), using affected relative-pair linkage analysis using gender and affected first-degree relatives information as covariates, showed strong evidence of linkage to a region near marker D19S433 on chromosome 19 (51.88 cM; *LOD* = 4.64) [24]. Using the same approach and using the same covariate models used in analysis of chromosome 19, the authors also identified a region on chromosome 4q31 near marker D4S1644 (140 cM; *LOD* = 3.73, $p = 0.0012$) [24]. In another genome wide scan in Dutch AAA families (101 affected sib-pairs from 58 families) linkage was confirmed to Chromosome 19q (multipoint linkage scores = 3.95) [25]. But it was observed that even though the locus mapped to the same chromosome 19q, the linkage region found in this group of patients did not overlap with the linkage regions reported previously for AAA. The disparate results may be due to many reasons such as genetic heterogeneity, differences in the analytical methods and inclusion or exclusion of covariates which might have led to the differences in the LOD scores [24,25].

A conventional family based linkage analysis approach requires inclusion of large families with affected individuals in at least three generation in the study. Even though DNA linkage analysis are unbiased and no prior knowledge is needed for the study, the