Platelet endothelial cell adhesion molecule-1 (PECAM-1) & coronary heart disease

Platelet endothelial cell adhesion molecule-1 (PECAM-1) is a 130-kDa member of the immunoglobulin superfamily of cell adhesion molecules. It is characterised by the presence of two immunoreceptor tyrosine-based inhibitory motifs (ITIMs) within its cytoplasmic domain that led to its recent assignment to the Ig-ITIM family of inhibitory receptors. PECAM-1 is expressed on the surface of circulating platelets, monocytes, neutrophils, particular T-cell subsets and endothelial cell intercellular junctions. PECAM-1 plays an important role in the adhesion of leukocytes by modulating the affinity of integrins and in their transendothelial migration. PECAM-1 is also involved in transmitting signals into the cell following its engagement, leading to negative regulation of platelet-collagen interactions. PECAM-1 has been shown to become phosphorylated at tyrosine residues Y663 and Y686 in response to many stimuli. When phosphorylated, these tyrosine residues support the binding of the Src homology 2 domain-containing protein tyrosine phosphatase (SHP-2), and may lead to alterations in binding characteristics of PECAM-1. In addition to its role in vascular cell adhesion, there is growing evidence that PECAM-1 can transduce signals that suppress programmed cell death which is thought to be via its ability to inhibit cytochrome C release from mitochondria after exposure of cells to a wide range of cytotoxic stimuli.

Several amino acid polymorphisms have been identified in PECAM-1. These are located in exon 3 at codon 80 altering a valine to a methionine (V80M), in exon 3 at codon 125 altering a leucine to a valine (L125V), in exon 8 at codon 563 altering an serine to a asparagine (S563N), and in exon 12 at codon 670 altering an arginine to a glycine (R670G). The latter three polymorphisms are in a strong linkage disequilibrium. Several of these polymorphisms were shown by a number of studies to be associated with risk of coronary artery disease (CAD) in an apparently contradicting way. Whereas the 125V allele of the L125V polymorphism (and usually the 563N and 670G alleles of the S563N and R670G respectively because of the strong linkage disequilibrium) has been shown to be associated with risk of CAD, the 125L allele (also the 563S and 670R alleles) was shown to be associated with risk of myocardial infarction (MI) (Table). Although these studies may seem to suggest conflicting data, those investigating the association of PECAM-1 polymorphism and risk of atherogenesis always show increased risk with certain haplotype (125V/563N/670G) regardless of ethnicity. On the other hand, studies looking at the association of PECAM-1 polymorphism and risk of MI always show increased risk with the other haplotype (125L/563S/670R) regardless of ethnicity. This is thought to be due to different effects of one or more polymorphisms in PECAM-1. As one variant is thought to alter PECAM-1-mediated transendothelial migration of monocytes leading to increased risk of atherosclerosis, the other variant/s is thought to modulate platelet activation leading to increased risk of MI.

In this issue, Fang and colleagues confirm previous studies looking at L125V polymorphism and risk of CAD, and suggest that L125V may influence PECAM-1-mediated transendothelial migration of monocytes during early atherogenesis. They provide...
the first evidence of such association in CAD patients of Asian Indian origin in Singapore after providing similar data in CAD patients of Chinese Singaporean origin. Although Fang et al. showed the same trend of association between S563N polymorphism and CAD, the results were not significant. This may be due to the strong linkage disequilibrium that was seen in other populations, but was not investigated by Fang et al.

Increased soluble levels of PECAM-1 (sPECAM-1) have been found in patients with severe congestive heart failure and acute MI. Fang and colleagues showed previously that subjects homozygous for 125V allele have higher sPECAM-1 levels in Chinese Singaporeans, and that sPECAM-1 was further correlated to sP-selectin, platelet count, and total white blood cell count. They suggested that platelets are a major source of sPECAM-1 and platelet activation and inflammation may contribute to PECAM-1 elevations in CAD patients. In this issue, Fang et al. provide the first evidence of higher levels of sPECAM-1 in CAD patients compared to controls in an Indian population sample, confirming previous data. Fang and colleagues confirmed the positive correlation between sPECAM-1 and sP-selectin, suggesting that PECAM-1 might be involved in platelet activation and subsequent thrombosis and MI. However, they showed no association between 125V allele and increased level of sPECAM-1 in the Indian population.

Over recent years, a number of studies have shown association between polymorphisms in adhesion molecules and risk of heart disease in a consistent manner. The situation with PECAM-1 is different. While one haplotype has been repeatedly reported to be associated with risk of MI, the other haplotype has been shown by a number of studies to be associated with increasing risk of atherosclerosis. PECAM-1 however is no ordinary adhesion molecules with its wide variety of functions in platelet activation, inflammation, cell survival, and the immune response. Whether this contradicting association is merely a chance or a genuine effect of each haplotype working differently on the pathology of heart disease, remains to be investigated.

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**Table.** List of studies looking at the association of PECAM-1 polymorphisms and risk of coronary artery disease (CAD) and myocardial infarction (MI)

<table>
<thead>
<tr>
<th>Stenosis</th>
<th>Origin</th>
<th>No. of patients</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wenzel et al, 1999</td>
<td>Germany</td>
<td>98</td>
<td>125V/563N associated with CAD &lt;50 yr</td>
</tr>
<tr>
<td>Gardemann et al, 2000</td>
<td>Germany</td>
<td>2500</td>
<td>125V associated with CAD in ‘low’ versus ‘high risk’ patients</td>
</tr>
<tr>
<td>Song et al, 2003</td>
<td>China</td>
<td>159</td>
<td>125V/563N associated with CAD</td>
</tr>
<tr>
<td>Elrayess et al, 2004</td>
<td>Finland</td>
<td>279</td>
<td>563N /670G associated with stenosis</td>
</tr>
<tr>
<td>Wei et al, 2004</td>
<td>Chinese Singapore</td>
<td>144</td>
<td>125V associated with CAD</td>
</tr>
<tr>
<td>Fang et al, 2005</td>
<td>Indian Singapore</td>
<td>137</td>
<td>125V associated with CAD</td>
</tr>
</tbody>
</table>

**MI**

| Sasaoka et al, 2001 | Japan         | 136             | 563S and 670R associated with MI              |
| Listi et al, 2004 | Italy         | 96              | 670R associated with MI                       |
| Elrayess et al, 2004 | UK            | 2037            | 563S and 670R associated with MI in smokers  |
References