A single nucleotide polymorphism (SNP) in the P-selectin gene produces the Thr715Pro missense mutation. This affects the last consensus repeat which is adjacent to the transmembrane domain. Previous studies demonstrated that carriers of the C allele, which encodes for proline, have lower soluble P-selectin levels (1). Miller et al. (2) in this issue of Thrombosis and Haemostasis examined whether this SNP is consistently associated with differences in plasma levels of soluble P-selectin (sP-selectin) between different ethnic groups (see pages 1060-5). This SNP was most frequent in Caucasians (11%), but less frequent in Asians (3%) and rare in people of African descent (<1%). sP-selectin levels were significantly lower (-25%) in the individuals with the AC or CC compared to the AA genotype in both whites and Asians. Nicely, there was a gene-dosage effect that was consistent throughout a number of subgroups, which may also affect sP-selectin levels (smokers, gender, age) (3).

Several questions arise: Where does sP-selectin originate, what is the clinical relevance of this P-selectin SNP and by which mechanism does it affect sP-selectin levels?

As demonstrated previously and reviewed recently (3), there is no convincing evidence that sP-selectin originates from endothelial cells (4-6), although some sP-selectin may come from alternative splicing. However, there is good evidence that activated platelets are a likely source of P-selectin and release sP-selectin in humans (7-9). Also, levels of sP-selectin are markedly higher in serum than in citrated blood, demonstrating that sP-selectin is released from platelets during clot formation (3). Hence, sP-selectin is considered an excellent and reproducible marker for platelet activation in humans (3). Although alternative splicing may also add to soluble forms of P-selectin, the contribution of this mechanism to an increase in sP-selectin levels is unknown. Further, it remains to be demonstrated whether sP-selectin serves any function in humans.

There was no significant association of this SNP with the presence of myocardial infarction or stenosis in a study comprising 250 patients in the UK (1). In contrast, only the Thr715Pro P-selectin SNP, but not a number of other P-selectin polymorphisms, was associated with myocardial infarction in about 650 patients of the ECTIM study in France/Ireland (10). These results have been published repeatedly in different journals, which could lead to a citation bias. One of these publications even provided only a p-value which was borderline significant (p = 0.054) (11). In contrast, in an even larger study in Germany, genotype distributions of this SNP did not differ between 870 patients with coronary artery disease as compared to controls (12).

Moreover, Barbaux et al. (12) showed similar sP-selectin levels in serum between patients and controls. In either group, individuals carrying the C allele had consistently lower (about 25%) serum sP-selectin levels (12). Although this is a suboptimal approach to obtain information on the in vivo activation of platelets, it supports the notion that this SNP may regulate the P-selectin contents of platelets. If this is the case this may potentially render platelets less adhesive, but differences in sP-levels between genotypes would not necessarily reflect differences in their in vivo activation. This needs to be further tested with platelet lysates.

Finally, recent data provide additional evidence that soluble P-selectin may enhance haemostasis (13, 14). Infusion of a recombinant P-selectin immunoglobulin (P-sel Ig) corrected the bleeding time in haemophilic mice, although a control Ig also stopped bleeding in 3 of 8 mice (15). The P-sel Ig also enhanced microparticle formation approx. 4-fold and tissue factor activity levels.
2-fold in plasma taken from three haemophilic patients. As there are fundamental differences in physiology between humans and mice (Louisiana Veterinary Medical Association, http://www.lvma.org/mouse.html) including many fold higher platelet counts in mice, it remains to be demonstrated whether soluble P-selectin or P-sel Ig can be therapeutically exploited in humans. However, these studies further support the concept that soluble P-selectin may not only be an innocent marker of in vivo platelet activation, but that it may in fact contribute to thrombosis and haemostasis. Further studies are therefore warranted to elucidate the role of soluble P-selectin and its genetic polymorphisms in various thrombotic diseases.

References