CYP2C9 exon 4 mutations and warfarin dose phenotype in Asians

It is well established that functionally defective variant alleles of CYP2C9 have a major impact on anticoagulation-related outcomes during warfarin therapy. A recent paper by Leung et al. reported the discovery of 4 new single nucleotide polymorphisms (SNPs) in the coding region of the CYP2C9 gene: L208V, Q192P, H184P, and I181L, with allele frequencies of 0.09-0.75 that may be associated with a low warfarin maintenance dose in Hong Kong Chinese patients. This report is consistent with previous studies showing that functionally defective variant alleles of the CYP2C9 gene can lead to reduced warfarin metabolism and lower achievable anticoagulation levels.

To the editor:

To critically assess the appropriateness of assigning acute leukemia diagnoses to patients with fewer than 10% (and in some cases, other causes of erythroid hyperplasia with slightly elevated blast counts also could be diagnosed incorrectly as acute erythroleukemia.

In assessing variations in the experimental protocols that might underlie the interlaboratory differences, we re-examined the primers used by Leung et al. The first 10 bases of the forward primer and 8 bases of the reverse primer (5’ to 3’) appeared to have been included to incorporate a unique restriction endonuclease site into the resulting amplicon. Analysis of the remaining primer sequence revealed that the forward primer exhibits a 100% match to exon 4/intron 4 sequences within CYP2C9, and CYP2C19. The reverse primer exhibits a 100% match to exon 4/intron 4 sequences within CYP2C9 and CYP2C19, although the 3’ end of the primer shows considerable identity to sequences with CYP2C18 and CYP2C19 and might well have resulted in some amplification at those loci as well. In any event, it is clear that the primers used by Leung et al. are not adequate for SNP discovery, as they will result in a mixed template from multiple loci. These observations call into question the presence of the L208V, Q192P, H184P, and I181L variants of CYP2C9 that may be associated with a low warfarin maintenance dose.
CYP2C9 and their association with a low warfarin dose phenotype in Asian patients.

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References

To the editor:

The role of erythrocyte peroxiredoxin in detoxifying peroxides and in stimulating potassium efflux via the Gardos channels

Using mice deficient in glutathione peroxidase, Johnson et al reported that this enzyme plays an important role within erythrocytes in the detoxification of organic peroxides.1 The authors extended the discussion to include another family of peroxide detoxifying enzymes, the peroxiredoxins. Far from being restricted to micro-organisms, as implied by Johnson et al, peroxiredoxin family members are widely spread throughout mammalian tissues, including erythrocytes and macrophages.2,3 Erythrocyte Prx II (also known as calpromotin, torin, natural killer enhancing factor B, thiol-specific antioxidant protein, or thioredoxin peroxidase B) reduces both hydrogen peroxide and organic peroxides, protects the membrane against lipid peroxidation, and derives its reducing power from the thioredoxin/thioredoxin reductase/nicotinamide adenine dinucleotide phosphate system.3 At an estimated 14 million copies per cell, Prx II is one of the most abundant erythrocyte proteins after hemoglobin.4

In a second mouse model, the Prx II gene has been deleted.5 These mice showed marked abnormalities, such as overloading of the spleen with iron and deposition of denatured globin precipitates within their erythrocytes. These data are consistent with excessive levels of peroxide, which are known to break down hemoglobin, releasing the iron from the protein in soluble complexes that can react with peroxides to generate cascades of damaging free radicals.6 Prx II therefore appears to help protect hemoglobin from free radical damage.

Studies performed with erythrocyte ghosts have demonstrated that Prx II plays a role in stimulating potassium efflux via the Gardos channels by interacting with the cytosolic surface of the plasma membrane.4 Prx II membrane association and Gardos channel activity are markedly up-regulated within sickle dense cells.7 Sickle dense cells exhibit classic symptoms of oxidative stress, such as the increased oxidation of membrane thiols and higher concentrations of the products of lipid peroxidation.8

Paradoxically for an antioxidant enzyme, a mixture of structural9 and biochemical studies10 have shown that Prx II itself can fall victim to rising levels of peroxide through the overoxidation of a catalytic cysteine residue to cysteine sulphinic acid. This overoxidation event inactivates the peroxidase activity. The molecular basis by which Prx II stimulates potassium efflux via the Gardos channels remains to be elucidated.

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References