LES ARTICLES SCIENTIFIQUES PUBLIEES PAR DOCTEUR OMER PLACIDE DOSSOU YOVO

1-

Hydroxycarbamide stimulates the production of pro-inflammatory cytokines by endothelial cells: Relevance to sickle cell disease.

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Pharmacogenet Genomics, 2010 Apr; 20(4):257-68.

Abstract

Background and Objective In sickle cell disease (SCD), hemoglobin S (HbS) polymerization renders red blood cells (RBC) both fragile and rigid and accounts for anemia and vasoocclusive crises (VOC). Abnormal RBC adhesion to vascular endothelial cells (VEC), in a context of chronic inflammation, cell activation, and vascular tone abnormalities, plays a key role in triggering VOC. Hydroxycarbamide (HC) is the only drug with a proven efficacy at decreasing VOC occurrence. HC decreases HbS polymerization by inducing fetal Hb expression but also RBC adhesive properties.

Methods We studied HC effect on the other cellular partner of adhesion, i.e. VEC. HC-induced TrHBMEC transcriptome variations were analyzed by microarrays both in basal and pro-inflammatory conditions. Among the endothelial HC target genes we focused on those related to the adhesion and inflammation pathways.

Results We found that HC had a significant effect on the later. Strikinly, it stimulates pro-inflammatory genes such as *IL1A, IL1B, IL6, IL8, CCL2, CCL5, CCL20* and *CCL8* both at the mRNA and protein levels. Similar data were also obtained with HPMEC and HUVEC primary cells.

Conclusions Our hypothesis is that HC propels the level of the pre-existing inflammation status of SCD patients over a threshold that results in a powerful cytokine-dependent hypothalamic-pituitary-axis mediated anti-inflammatory response.

2-

Effects of RANTES and MBL2 gene polymorphisms in sickle cell disease clinical outcomes: Association of the g.In1.1T>C RANTES variant with protection against infections.

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Abstract

Sickle cell anemia (SCA) is a single-gene mutation genetic disease characterized by a highly variable clinical presentation. Genetic modifiers of the general outcome have been reported, some of them linked to the a- and b-globin gene clusters. In addition, polymorphisms linked to various

genes have been associated with specific complications of the disease. We studied the polymorphisms of two candidate genes, MBL2 (Mannose-Binding Lectin 2) and chemokine RANTES (Regulated upon Activation, normal T cell-Expressed and Secreted), in relation to Infectious complications in a series of 115 patients with SCA living in two different environments: Benin and France. All the patients were identified at birth and followed for 5 years. All were homozygotes for the bS Benin haplotype. Our results show no association of MBL2 variants with infectious events, but we observed for the first time that patients carrying the g.In1.1C RANTES variant had a lower risk of recurrence of bacterial infections, suggesting a protective effect conferred by the variant.

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Variants of the Mannose-Binding Lectin Gene in the Benin Population: Heterozygosity for the p.G57E Allele May Confer a Selective Advantage.

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Abstract

Human mannose-binding lectin (MBL) plays an important role in innate immunity.MBLdeficiency is associated with mutations in the promoter region and in exon 1 of the *MBL2* gene. Such deficiency has been correlated with elevated incidence of infections in infancy and in immunocompromised adults. We determined the distribution profile of the *MBL2* gene variants in the general population of Benin (West Africa) and in a vulnerable subset of children with sickle cell disease (SCD) (*SS* homozygotes). Five hundred fortytwo healthy individuals (274 newborns, 268 adults) and 128 patients with SCD (35 newborns, 93 children) were screened for the common variant alleles in the *MBL2* secretor haplotype region (exon 1 and promoter). The p.G57E variant allele was the most frequent allele compared to p.G54D (27.5% vs. 1.6%, respectively). The p.R52C allele was not found in this population. There was no difference in allele or genotype frequencies between healthy newborns and newborns with SCD. Alleles associated with MBL deficiency were more frequent in adults than in newborns (69.8% vs. 57.3%, respectively; $p = 0.002$). This enrichment was exclusively due to an elevated proportion of heterozygotes for the p.G57E allele (47.0% vs. 35.3%, respectively; $p = 0.004$), supporting a potential selective advantage of this genotype. Our results, compared to those reported in other African countries; support the implication of the *MBL2* gene in various major infections in Africa, such as meningitis and tuberculosis in HIV-positive patients.

LE DEPISTAGE GRATUIT DU DIABETE