The rationale for using hydroxycarbamide in the treatment of sickle cell disease" (Haematologica 2011;96:488-491). *Reply*

Rees's elegant review of the utility of hydroxycarbamide in sickle cell disease (SCD) concludes with the wish that other drugs to ameliorate SCD would soon be found.[1] One such may be hiding in plain sight: a double blind controlled study of the treatment of sickle patients with n-3 fatty acids found that they reduced the frequency of vaso-occlusive crisis (VOC) from 7.8 to 3.8 events/year (P<0.01). That trial was undertaken under the hypothesis that n-3 fatty acids would inhibit the coagulopathy that accompanies vaso-occlusive events.[2] Perhaps because of this underlying rationale the study has received scant attention because there are numerous other negative trials of anticoagulation and anti-platelet interventions in SCD.[3]

However, it is now apparent that the effects of n-3 fatty acids extend beyond interfering with a coagulopathy. n-3 fatty acids replace the prior acyl chains in the red blood cell (RBC) phospholipids including those of phosphatidylserine (PS).[2] The latter is normally confined to the inner layer of the RBC membrane. When sickle RBCs are deoxygenated, PS shifts to the outer layer.[4] Sickle RBCs are abnormally adhesive (a factor in VOC) in part because of exteriorized PS. There is a close correlation between PS on the RBC surface and adhesion to endothelium; there is direct binding of PS bearing RBC to specific endothelial receptors.[5]

The assymetric transmembrane distribution of phosphatides in the RBC is enzymatically regulated and is strongly modified by the saturation of the phosphatide's acyl chains, changing as much as 12-fold when the number of double bonds in the acyl chain is varied.[6] Since the saturation of acyl chains of PS is changed by the n-3 fatty acids, it is likely that its transmembrane redistribution with sickle RBC deoxygenation would also be changed. Thus the effect of n-3 fatty acids on RBC adhesion in SCD may account for its beneficial effect and so renewed attention to n-3 fatty acids seems warranted.

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