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Journal club

UNCLOGGING SICKLE CELL ANAEMIA

In 1949, the molecular basis of a disease was identified for the first time, that of sickle cell anaemia, by Pauling, Itano and colleagues. Since then, generations of students were taught that the substitution of a specific glutamate with valine in the β-globin protein results in polymerization of haemoglobin. This polymerization produces the deformed sickle-shaped red blood cell or 'sickle erythrocyte' that is characteristic of this disease, which affects millions worldwide.

However, this intracellular disease aetiology belies the complex cell surface interactions that orchestrate the pathogenesis of acute sickle cell anaemia. Occlusion of the small blood vessels in sickle cell anaemia is extremely painful and can be life-threatening. The initial event in vaso-occlusion is the reduced passage of sickle erythrocytes through capillaries, but activation of endothelial cells and platelets follows soon after. This leads to adhesion of erythrocytes and leukocytes to the endothelium in the form of multicellular aggregates, and to the amplification of vaso-occlusion — like a multi-vehicle accident blocking a highway.

> "blocking P-selectin with an antibody reduces… complications of vaso-occlusion in sickle cell anaemia"

The hypothesis that cell surface interactions mediate the formation and adhesion of these multicellular aggregates led to a hunt for surface proteins involved in this process. P-selectin is found in storage granules of resting endothelial cells and platelets and translocates to the cell surface upon activation of these cells by inflammation. P-selectin is also required on the endothelial cell surface for adhesion of sickle erythrocytes to the endothelium.

As we followed this field over many years, we were intrigued to see these important discoveries translated into potential therapies. Recently, Ataga and colleagues reported that blocking P-selectin with an antibody reduces the frequency of acute complications of vaso-occlusion in sickle cell anaemia. These results make sense, as decreasing the adhesion-promoting cell surface interactions of P-selectin would be predicted to reduce vaso-occlusion.

Cell surface proteins have long been a fascinating focus of cell biology research, by illuminating how cells interact with their environment. It is exciting to see the importance of a fundamental cellular process confirmed in human clinical studies, and all the more thrilling that these studies can ultimately benefit individuals with a severe inherited disease.

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ORIGINAL ARTICLES Pauling, L. *et al.* Sickle cell anemia, a molecular disease. *Science* **110**, 543–548 (1949) | Matsui, N. M. *et al.* P-selectin mediates the adhesion of sickle erythrocytes to the endothelium. *Blood* **98**, 1955–1962 (2001) | Ataga, K. I. *et al.* Crizanlizumab for the prevention of pain crises in sickle cell disease. *N. Engl. J. Med.* **376**, 429–439 (2017)