

Basic Research Project: Activation of cAMP-mediated Sickle Cell Adhesion

Agonist-induced signaling is a primary mechanism regulating adhesiveness of platelets, leukocytes and other cells. However, RBCs are generally considered to be inert to agonist stimulation; thus signaling in sickle (SS) RBCs by agonists to directly activate SS RBC adhesiveness is relatively unexplored. Because abnormal SS RBC adhesion is believed to contribute to the painful vaso-occlusive crises suffered by sickle cell patients, it is crucial to understand mechanisms that modulate this adhesion. We recently made the important finding that SS RBCs are very responsive to agonist stimulation, resulting in a rapid and pronounced increase in adhesion to multiple vascular proteins. Here we propose to expand upon our findings that agonist-induced cAMP production results in a protein kinase A-dependent activation of SS RBC adhesion to laminin. Thus, epinephrine and several other physiologic agonists rapidly increase SS RBC adhesion in a subset of patients, providing a potential physiologic link between conditions that elevate these agonists, such as stress and pain, with vaso-occlusion.

We propose to expand upon these findings with the following specific aims designed to:

1. Establish the basis for epinephrine-responsive and non-responsive RBCs from different sickle cell patients.
2. Identify the epinephrine receptor subtype(s) that stimulate SS RBC adhesion and identify additional naturally occurring agonists and agonist receptors that induce this process.
3. Map the cAMP-dependent signaling pathway(s) mediating stimulated sickle cell adhesion to laminin.
4. Identify additional vascular proteins that support cAMP-stimulated SS RBC adhesion and the receptors/sites mediating these adhesive interactions.
5. Determine the role of cAMP-stimulated SS RBC adhesion in an *in vivo* system.

These studies are likely to lead to new therapeutic targets for the disruption of cAMP-mediated adhesive interactions in sickle cell patients.