

James & Esther King Biomedical Research Program

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*2006 Program
New Investigator (3-year project)*

Project Title: Biophysical Determinants of Leukocyte Transmigration

Project Summary: Cigarette smoking is a leading cause of heart disease. Heart disease is the number one killer in the United States causing nearly 2,500 deaths every 35 seconds. One of the underlying causes of heart disease is the formation of fatty streaks also referred to as lesions on the lining of blood vessels. The buildup of these fatty streaks can eventually restrict blood flow through partial blockage of the blood vessels. Fatty streaks first form in childhood and progress to larger raised lesions in adolescence and young adulthood. The extent of these lesions is greatly increased by a number of risk factors, including smoking. Smokers have an increase in fatty streaks and raised lesions in the aorta, the main blood vessel bringing oxygenated blood from the heart to the body, and in the coronary arteries, which supply blood to the heart muscle. The fatty streaks are mainly composed of white blood cells located under the lining of the blood vessels. Their formation is initiated during inflammation when white blood cells are recruited to a site of injury. This recruitment process involves three major steps. First, the cells roll on the blood vessel lining, eventually stop, and firmly stick to it. The blood vessel lining is composed of another cell type referred to as endothelial cells. Once the white blood cells are stopped, they migrate through a junction between the endothelial cells. These junctions are very tight and regulate the migration of the white blood cells into inflamed areas through a complex process that is still not fully understood. The junctions are stabilized by adhesion receptors. In order for a white blood cell to cross this junction, it must interact with these receptors. This interaction is made possible by adhesion receptors on the surface of the white blood cell, which can stick to their counterparts found on the endothelial cells that form the junction. The long-term goal of this project is to understand the biophysical properties of the endothelial cell junctions in the presence and absence of inflammation. I will achieve this goal by first looking at the contribution of the different adhesion receptors in maintaining the integrity of the endothelial junction. I will also determine how inflammation facilitates migration of the white blood cells through the junctions. The proposed studies will bring essential basic scientific knowledge that will help in the development of better therapies against blood vessel damage exacerbated by cigarette smoke.