THE ROLE OF NOVEL CYTOSKELETAL ASSOCIATIONS ON THE FUNCTION OF THE SELECTIN AND INTEGRIN FAMILIES OF ADHESION MOLECULES

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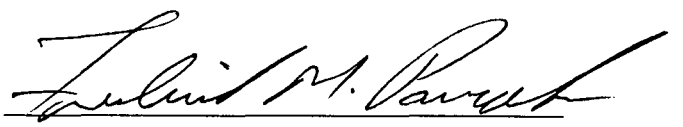
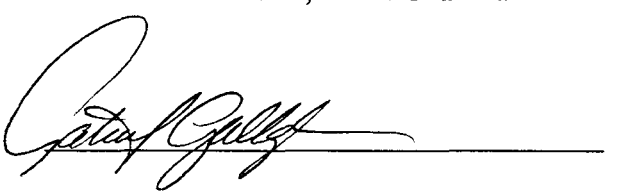
Doctoral

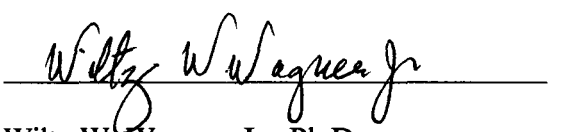
Committee



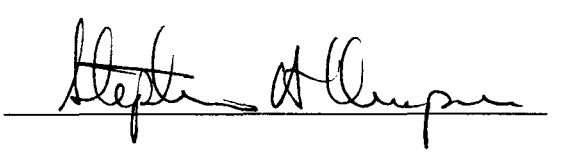
Fredrick M. Pavalko, Ph.D. Chairman



Patricia J. Gallagher, Ph.D.



Wiltz W. Wagner, Jr., Ph.D.



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ABSTRACT

To participate in normal processes such as the inflammatory response, wound healing, and embryogenesis, cells must be able to regulate their adhesion, specifically the actions of attachment and detachment. Regulation of adhesion also plays a significant role in pathological processes such as cancer metastasis, rheumatoid arthritis, and ischemia/reperfusion injury. If the regulatory mechanism that results in attachment to and detachment from other cells or extracellular matrices was defined, there would exist the potential for improved therapeutic intervention in many adhesion-related diseases.

During a normal response to infection, three families of adhesion molecules, selectins, integrins, and select members of the immunoglobulin superfamily play crucial roles in leukocyte adhesion to the endothelial lining of blood vessels in the vicinity of infected tissues (1). The leukocytes, free-flowing in the blood stream, must have a mechanism whereby they slow their movement, adhere tightly to the blood vessel wall, and then migrate out of the blood into the surrounding, infected tissue. A three step model proposed by Springer in 1994 (2) describes the roles of selectins, integrins, and chemoattractants in the subsequent leukocyte emigration that follows an inflammatory response. There are different combinations of selectins, integrins, and chemoattractants possible allowing for great diversity in signaling mechanisms and possibly for selectivity of leukocyte recirculation and migration into inflamed tissues (2). The hypothesis that integrin and selectin families of adhesion molecules mediate their adhesive function during the inflammatory response through interactions with novel and known cytoskeletal proteins was

investigated. I have found that α-actinin associates directly with the cytoplasmic tails of all three selectin molecules. Talin, paxillin, actin, and myosin IIa also associate with the selectin tails. However, it is not known whether these proteins are indirectly associated through α-actinin or if there is a direct association between these individual cytoskeletal proteins and selectin cytoplasmic tails. Vinculin associates with the cytoplasmic tail of L-selectin, but an association with E- and P-selectin is not evident. A newly described protein called embryonic myosin light chain kinase was found to associate with the cytoplasmic tails of L-, E-, and P-selectin, as well as for β_1 and β_2 integrins.

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