Chapter 2

The Vascular Endothelium

A New Actor in the Pathogenesis of Vascular Injury in Systemic Lupus Erythematosus

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1. Introduction

During the past twenty years the paradigm for the pathogenesis of inflammation has undergone a revolution. Although the effector functions of leukocytes remain paramount in the pathogenesis of inflammation, the endothelial cell, once thought to be a passive bystander, is now recognized as one of the central, active participants in the inflammatory process. The endothelium dictates the site of inflammation and the types of cells involved in the inflammatory response by expressing molecules on their surface that preferentially bind to one or another subtype of circulating leukocyte exclusively at inflamed sites. Moreover, the vascular endothelium is a secretory organ capable of synthesizing and secreting many different inflammatory mediators. The role of endothelial cells in the pathogenesis of systemic lupus erythematosus (SLE) is only now receiving the attention it is due, and as our understanding increases, it is likely that new approaches to SLE therapy will result. This chapter reviews the role of the endothelial cell in the pathogenesis of inflammation, the known effects of SLE on the vascular endothelium, and what is currently understood about the role of the vascular endothelium in the pathogenesis of SLE.

2. The Vascular Endothelium During Inflammation

Leukocytes emigrate only from postcapillary venules in most vascular beds. The specific localization of leukocyte emigration has been explained, in part, by the relatively slow speed of the cells in the circulation in postcapillary venules, and by the difficulty leukocytes have in undergoing further deformation within the capillaries. However, it is now clear that the restriction of adhesion molecule ex-
ENDOTHELIAL ACTIVATION IN SLE

Fig. 1. Endothelial activation in SLE. C1qR, C1q receptor; IC-C1q, immune complex-C1q conjugates; CD40L, CD40 ligand; Anti-EC Ig, antiendothelial cell antibodies; IC, immune complex; C' activation, complement activation; PMN, polymorphonuclear leukocyte.

pression to the endothelium of the postcapillary venules is critical for the emigration of leukocytes from the vasculature exclusively at the level of the postcapillary venule (Fig. 1).

Three major families of proteins are expressed on the surface of either leukocytes or endothelium that play a role in leukocyte-endothelial interactions. The integrins are a family of heterodimeric adhesive proteins expressed on leukocytes. Monocytes and lymphocytes express the β1 integrin VLA-4 (CD49d/CD29). All leukocytes express one or more of the β2 integrins, a group of related heterodimeric adhesive proteins that share a common β chain (CD18) but differ with respect to their α chains (CD11a,b,c). The integrins bind to proteins on the surface of the endothelium (and other cells) that belong to the immunoglobulin superfamily (ICAM-1, ICAM-2, and VCAM-1). A third family of adhesive proteins that binds to carbohydrate residues on glycoproteins and glycolipids has recently been described (selectins). Three distinct molecules comprise the selectin family: P-selectin, E-selectin, and L-selectin. P-selectin is expressed on stimulated platelets and endothelium, L-selectin on leukocytes (neutrophils, monocytes, and a subset of lymphocytes), and E-selectin on stimulated endothelium, respectively. E-selectin and P-selectin both bind to glycoproteins and glycolipids that contain Sialyl Lewis X antigen (a complex carbohydrate). Sialyl Lewis X antigen is expressed predominantly on the surface of neutrophils (reviewed in refs. 1–3)).

Histamine and thrombin, agents released and generated rapidly at inflamed sites, stimulate the translocation of preformed P-selectin from Weibel-Palade bod-