Anti-PMN Leukocyte Strategies and Their Application to Focal Cerebral Ischemia*

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In capillaries, the physical properties of individual cells contribute significantly to the rheology of blood and to organ perfusion. In this summary we consider the biophysical properties of circulating cells that determine their motion in the microcirculation and its disturbance in ischemia. The focus is on polymorphonuclear (PMN) leukocytes, their deformability, adhesive properties and cytotoxicity. The intravascular pool of PMN leukocytes will be considered and the mechanism of the non-reflow phenomena in the cerebral microcirculation.

The Kinetics of PMN Leukocytes in the Microcirculation

In the past decade, a body of evidence has accumulated which suggests that despite relatively small numbers in the circulation, PMN leukocytes may be involved in a wide range of cardiovascular complications in addition to classical inflammatory reactions and host defense. The distinction between a beneficial role and an injurious role of granulocytes to the host has become blurred and no organ may escape the potentially cytotoxic effects of these circulating activated cells. Insights have come from a range of approaches. Biophysical and biochemical studies have shown that leukocytes are made up of a relatively stiff viscoelastic actin-containing cytosolic matrix that is difficult to deform by the fluid stresses in the circulation. Furthermore, the cells have the ability to polymerize, which leads to further stiffening of the cell cytoplasm [25]. Granulocytes are larger than other circulating cells, yet they need to pass through capillaries which may be as narrow as almost half their resting dimension. PMN leukocytes can adhere readily to vascular endothelium and other substrates by a mechanism which includes adhesion glycoproteins, such as the in-

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tegrins CD11a,b,c/CD18 and several selectins [1, 13, 20]. The underlying molecular mechanisms may involve different membrane adhesion energies and cell activation of both PMN leukocytes and endothelial cells. These conditions may lead to microvascular entrapment of granulocytes with capillary occlusion and an associated capillary "no-reflow" phenomenon during pathophysiological states, and accumulation of neutrophils in postcapillary venules [23]. Attachment of neutrophils and monocytes to the endothelium causes elevation of endothelial and microvascular permeability [38] by a mechanism which involves the adhesion glycoproteins [3]. Release of oxygen free radical products occurs as a result [30].

Even under normal physiological conditions, the presence of PMN leukocytes in microvessels causes disturbance of microvascular flow. Their entry time into the orifices of capillaries with single file flow is considerably longer than that of the more flexible red cells [37]. The entry deformation depends critically on the pressure drop across the cell and the dimension of the capillary channel [22] (Figs. 1, 2). After entry into capillaries, PMN leukocytes move with a lower velocity than red cells, a condition that leads to a cellular train formation, i.e., a leukocyte with high numbers of erythrocytes accumulated upstream and a cell-depleted region downstream [23]. The significance of the cell transformation lies in the fact that the hemodynamic resistance in such capillary vessels is elevated [33], which in turn manifests itself by a significant eleva-