M4 ADP-RIBOSYLTANSFERASE-I AND LEUCOCYTE CHEMOTAXIS
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Arginine-specific ADP-ribosyltransferase (ART1) cleaves NAD+ and transfers a free ADP-ribosic group to selected Arg residues on target proteins. cDNA encoding ART-1 was first cloned from skeletal muscle, and the enzyme shown to be anchored to the outer aspect of the plasma membrane by a GPI linkage. We have shown that ART1 is also expressed in human PMNs, and have identified 2 polymorphisms in the human sequence, encoding Pro357→Leu and Thr392→Ser. Human ART1 has now been expressed as a fusion protein with glutathione S-transferase in a baculovirus expression system, and antibodies were raised against the fusion protein which recognized authentic ART-1 on the surface of PMNs. Exposure of PMNs to FMLP, PAF or IL-8 was shown to trigger blocked by a panel of inhibitors of the catalytic activity of ART1 to the cell surface (T412 (vitamins K1 and K3, novobiocin and nicotinamide) as well as pseudosubstrates of the enzyme (agmatine and DEA-BAG), and there activity in PMNs did not alter the magnitude of chemotaxin-dependent gradient. The likely molecular target is the extracellular domain of a ART1 activity and F actin assembly (r2 to the ART1 is implicated in the pathway mediating chemotaxis by surface integrin which serves a role (i) to anchor actin-containing microfilaments of the cytoskeleton to the plasma membrane, and (ii) in adhesion to extracellular matrix or other cells.