THE ROLE OF PDGF-BB, LYSOPHOSPHATIDIC ACID, AND PROTEOLYTIC ACTIVITY IN THE INVASIVE BEHAVIOR OF HUMAN BRAIN VASCULAR PERICYTES

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Recruitment of pericytes is needed to stabilize new vessels formed during angiogenesis or vasculogenesis. Although important to the viability of the vessel, information on how the pericytes are recruited to blood vessels is lacking. It is believed that molecules produced by endothelial cells lining the blood vessel walls influence pericyte recruitment. Both the upward and downward invasion of human brain vascular pericytes (HBVPs) through 3D collagen gels was tested in the presence of different endothelial cell produced factors. Of the molecules tested, platelet-derived growth factor-β (PDGF-BB) was found to be the most important in signaling HBVPs to invade in a 3D collagen matrix. Invasion can further be enhanced through synergism of PDGF-BB with lysophosphatidic acid (LPA), an activator of G protein signaling. When given together these two molecules increase invasion up to two times that of PDGF alone. The use of pertussis toxin, which blocks the activity of LPA, and recombinant soluble PDGF-receptor beta which traps and blocks PDGF-BB, were able to significantly block invasion in response to PDGF and LPA and provide further support for their functional role in HBVP invasive behavior. Invasion can also be blocked by using GM6001, a matrix metalloproteinase (MMP) inhibitor, demonstrating a requirement for MMP activity during this response. This work further elucidates mechanisms underlying how pericytes invade and migrate toward developing blood vessels to regulate capillary tube assembly and maturation in 3D extracellular matrix environments.