19. Modulation of angiogenesis in zebrafish embryos by sphingolipids

Toshiro Okazaki (Tottori University)

Treatment with thalidomide induced the defect of major blood vessels in the development of zebrafish embryo. In thalidomide-induced inhibition of angiogensis intracellular ceramide was increased by activation of neutral sphingomyelinase (nSMase), while synthetic cell permeable ceramide *N*-acetylsphingosine (C2-ceramide) also inhibited angiogenesis of the embryo. In contrast, sphingosine-1-phosphate (S1P) restored thalidomide or C2-ceramide-induced inhibition of angiogenesis through inhibition of nSMase-dependent ceramide generation. Injection with anti-sense morpholino oligonucleotides for nSMase restored thalidomaide-induced inhibition of embryonic angiogenesis with inhibition of ceramide generation. In human umbilical vein endothelial cells (HUVECs), anti-angiogenic action of thalidomide was similarly mediated through inhibition of neuropilin and Flk-1 expression regulated by ceramide and S1P through nSMase. These results suggest that the balance between ceramide and S1P through nSMase regulates anti-angiogenic properties of thalidomide by inhibition of neuropilin and Flk-1 expression in vascular endothelial cells of the zebrafish embryo.