Discovery of Antiangiogenic Agents from Fungal Metabolites

Jeong-Hyung Lee, Yun-Joo Park, Hang-Sub Kim and Jung-Joon Lee
Anticancer Research Laboratory, Korea Research Institute of Bioscience & Bitechnology
Taejeon Korea

Angiogenesis, the formation of new capillary blood vessels derived from pre-existing vasculature, is a complex process involving extensive interplay between cells, soluble factors, and ECM components. In the adult, the proliferation rate of endothelial cells is very low compared with that of many other cell types in the body. Physiological exceptions in which angiogenesis occur under tight regulation are found in the female reproductive system and during wound healing. Unregulated angiogenesis may contribute to a number of pathological processes such as rheumatoid arthritis, diabetic retinopathy, and tumor growth and metastasis. Recent accumulating evidences indicate that inhibition of angiogenesis is a valuable strategy to treat, so called angiogenic diseases such as tumor. In our search for anti-angiogenic agents from fungal metabolites, we isolated two new compounds, AGI-4 and AGI-7, from *Aspergillus* sp. by bioassay-guided fractionation and isolation. AGI-7 was isolated as an inhibitor of capillary-tube formation of HUVECs on Matrigel matrix with IC50 of 200 ng/ml. AGI-7 also inhibited the formation of new blood vessel *in vivo* measured by CAM assay. Furthermore, the migration and invasion of cultures HUVECs was significantly suppressed by AGI-4, implying that AGI-7 could exert its anti-angiogenic activity through the inhibition of migration of HUVECs. Another inhibitor, AGI-4 isolated as an inhibitor of VEGF-induced HUVECs proliferation, dose-dependently inhibited the proliferation of HUVECs induced by VEGF with IC50 of 300 ng/ml. AGI-4 significantly suppressed VEGF-induced new blood vessels through the Matrigel plug *in vivo* assessed by mouse Matrigel plug assay. Furthermore, administration of AGI-4 to C57BL6 mice bearing 3LL or B16BL6 cells elicited significant antitumor activity in a dose-dependent manner. Taken together, these results indicate that both AGI-4 and AGI-7 could be useful lead compounds to develop novel antiangiogenic agents.