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Development of the humanized anti-MIC-1 monoclonal antibody repressing tumor angiogenesis in colon and prostate cancer xenograft models

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The macrophage inhibitory cytokine-1 (MIC-1) is a member of transforming growth factor beta (TGF-β) superfamily and its expression has been shown to associate with several human cancers including breast, colon, and prosate cancers. MIC-1 expression/secretion has also been found to be increased by the hypoxic conditions in many cancer cell lines. Through various angiogenic assays, we have found that MIC-1 promotes angiogenesis by stimulating endothelial cells via the PI3K/Akt and ERK signaling pathways. In a mouse melanoma model, tumors derived from high MIC-1-expressing cells displayed faster growth and higher blood vessel formation than ones from low MIC-1-expressing cells, implicating that MIC-1 contributes to tumor growth by promoting tumor angiogenesis. To develop antibodies blocking pro-angiogenic activity of MIC-1, we have generated mouse hybridoma clones and selected two clones that produce antibodies with high affinity to the human MIC-1. One of these two antibodies effectively blocked MIC-1 function of stimulating endothelial cells. Also, in a mouse melanoma model, intravenous administration of this anti-MIC-1 antibody inhibited tumor growth and angiogenesis. Next, an anti-MIC-1 humanized antibody expression vector was constructed from the mouse clone by CDR grafting, while retaining murine framework residues that influence the antigen-binding activity. The anti-MIC-1 humanized IgG produced in the vector-transfected CHO cells was able to block MIC-1-induced angiogenesis. Futhermore, this humanized anti-MIC-1 antibody was also capable of inhibiting tumor growth and intratumor blood vessel formation in colon and prostate cancer xenograft models. Overall, the present study suggests that anti-MIC-1 humanized monoclonal antibody could be therapeutically useful for angiogenesis-related diseases including cancer.

Biography

Hansoo Lee completed his PhD program from State University of New York at Buffalo, USA (1990). He went on to pursue 2-year Postdoctoral studies from Memorial Sloan-Kettering Cancer Center at New York. Since 1992, he has been a Professor of Kanwon National University in South Korea. He has published almost 100 papers in reputed journals and is currently working as the Director of Medical and Bio-Material Research Cencer, a regional core research organization funded by Korean Government.

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