

Molecular mechanism of liver metastasis

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Intrasplenic administration of a colon adenocarcinoma cell line, colon 26, induced tumor necrosis factor (TNF) α protein expression around the central and portal veins of the liver at 3 days, and liver metastases by 24 days after the tumor injection, in 90% of wild-type (WT) mice. To explore the roles of TNF- α in the process, we administered colon 26 cells into TNF receptor p55 (TNF-Rp55) knockout (KO) mice. Less than 50% of TNF-Rp55 KO mice developed liver metastasis with significantly lower liver weights and the volumes of metastatic foci. These observations suggest the critical roles of TNF-Rp55-mediated signals in this liver metastasis model. The intrasplenic tumor injection induced mRNA expressions of vascular endothelial growth factor, heparin-binding epidermal growth factor, matrix metalloproteinase-9, and tissue inhibitor of matrix metalloproteinase-1 at similar levels in the livers of both WT and TNF-Rp55 KO mice. Immunohistochemical analyses of the livers of WT mice after tumor injection demonstrated the enhanced expression of vascular cell adhesion molecule (VCAM)-1 and E-selectin on sinusoidal endothelial cells. Enhanced E-selectin expression was similarly observed in the liver of TNF-Rp55 KO mice after tumor injection. However, the enhancement in VCAM-1 mRNA expression and its protein production was significantly attenuated in the liver of TNF-Rp55 KO mice when compared with WT mice. Finally, in WT, intrasplenic injection of colon 26 induced TNF- α , IL-1 α , and IL-1 β mRNA expression in liver. On the contrary, in TNF-Rp55 KO, TNF- α but neither IL-1 α nor IL-1 β expression, was attenuated in liver after the intrasplenic injection, compared with WT. Collectively, these observations suggest that TNF-Rp55-mediated signals have a positive feedback loop and can up-regulate VCAM-1 expression in the liver, leading to subsequent liver metastasis after intrasplenic tumor injection.

Reference

Kitakata, H., Nemoto-Sasaki, Y., Takahashi, Y., Kondo, T., Mai, M., and Mukaida, N. (2002) Essential roles of tumor necrosis factor receptor p55 in liver metastasis of intrasplenic administration of colon 26 cells. *Cancer Res.* 62: 6682-6687.