Essential contribution of tumor necrosis factor receptor (TNF-R) p55-mediated signals in metastasis and carcinogenesis

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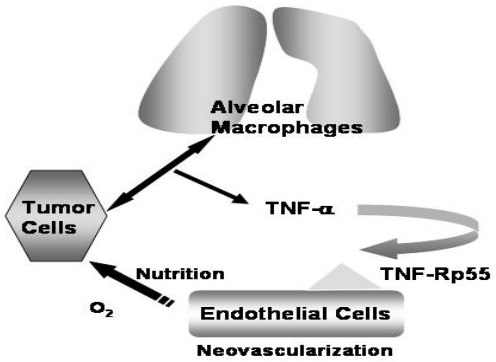
We have previously demonstrated that TNF-Rp55-mediated signals could up-regulate the expression of an adhesion molecule, vascular adhesion molecule (VCAM)-1 in sinusoidal endothelial cells and eventually facilitate liver metastasis by intrasplenic injection of a colon carcinoma cell line into mice (1).

Intravenous injection of a mouse renal carcinoma cell line, Renca, caused a large number of lung metastasis foci in wild-type mice, with TNF-α protein at tumor sites. Metastasis foci expanded at similar rates in both wild-type and TNF-Rp55-deficient mice until 21 days after the injection. On the contrary, later than 21 days, metastasis foci regressed spontaneously in TNF-Rp55-deficient mice, but not wild-type mice. Concomitantly, the number of apoptotic tumor cells were greater in TNF-Rp55-deficient mice, whereas neovascularization was less evident in TNF-Rp55-deficient mice than wild-type mice, with depressed expression of a potent angiogenic factor, hepatocyte growth factor gene in TNF-Rp55-deficient mice (2) (see below Figure). These observations implied that TNF-Rp55-mediated signals have distinct but important roles in metastasis to liver and lung.



Mice developed multiple adenomatous lesions in colon after repeated oral intake of dextran sulfate sodium solution, following an intraperitoneal injection of a potent chemical carcinogen, azoxymethane. The same treatment caused few adenomatous lesions in TNF-Rp55-deficient mice. Because this model may recapitulate adenocarcinoma developed in patients with chronic ulcerative colitis, TNF-Rp55 may be a good molecular target for preventing this severe complication in chronic colitis.

References

1. Kitakata H et al. Cancer Res.62: 6682, 2002.
2. Tomita Y et al. Intl. J. Cancer 112: 927, 2004.