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Interaction of colon carcinoma cells with rat hepatic sinusoidal cells during early stages of metastasis

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In our country, the majority of colorectal cancer patients develop and die with liver metastasis. Chemotherapy, radiotherapy and resection do not provide effec tive therapy for this disease. We therefore study the possibilities to enhance the hepatic immune system and the defense against metastasizing colon carcinoma cells. Pit cells, one of the sinusoidal cells in the liver, display spontaneous cytolysis of colon carcinoma cells and therefore are considered to be natural killer (NK) cells. Isolated pit cells can be divided into equal subsets with low (LD) or high density (HD). HD-NK cells have several characteristics which are intermediate between blood NK cells and hepatic LD-NK cells, suggesting that blood NK cells marginate in the liver, develop into HD-NK cells and later into LD-NK cells. LD-NK cells possess up to six times higher NK activity against different tumor cell lines as compared to blood or spleen NK cells, thereby reaching the level of lymphokine-activated killer (LAK) cells. Blood NK cells and hepatic HD-NK cells, but not LD-NK cells, can be activated to higher levels of cytotoxicity by several cytokines and biological response modifiers. This opens the possibility to activate the population of hepatic NK cells. Pit cells in normal live rare probably activated by their cohabitation with Kupffer cells, which are able to secrete a number of cytokines. Moreover, pit cells appear to be dependent on the presence of Kupffer cells, because specific removal of these cells by Cl_2MDP-liposomes, makes the pit cells disappear within 2 wk, suggesting a life span of two wk for pit cells. With regard to the killing mechanism, we have routinely measured about 40% specific ^{51}Cr-release after coculturing colon carcinoma cells with pit cells, indicating membrane damage or cytolysis. Recently, we also observed the induction of apoptosis in colon carcinoma cells by pit cells, as shown by chromatin condensation, nuclear fragmentation, DNA fragmentation and DNA ladder.

Several *in vivo* studies have reported almost complete efficiency (> 99%) in the killing of tumor cells within two days after a mesenteric injection of tumor cells. We have observed the adherence of pit cells and Kupffer cells to tumor cells shortly(1 h)after injection. At this time interval, large numbers of tumor cells are phagocytosed by Kupffer cells, probably after interaction with pit cells. Few tumor cells (< 1%), however, succeed in escaping from the de fense system and develop secondary tumors.

Normal Kupffer cells are unable to kill tumor cells. Recent evidence, however, indicates that cocultures of Kupffer cells and pit cells display greatly enhanced killing of colon carcinoma cells.

Single tumor cells get stuck in the sinusoids when entering the liver, because their size largely exceeds the diameter of a sinusoid. After this, their adhesion molecules might react with the surface molecules of the endothelial cells, enabling them to extravasate and enter the liver parenchyma. We suppose therefore, that the adherence of endothelial cells and tumor cells, might as well be crucial in early stages of hepatic metastasis.

Later stages of growing metastasis are supposed not to involve sinusoidal cells. Instead, other members of the cellular immune system, such as cytotoxic Ylymphocytes, tumor-infiltrating lymphocytes, monocytes and monocyte-derived macroph ages may then play a defensive role.

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