Chapter 9

General discussion
Liver metastases from colorectal cancer is still the main cause of death in colorectal cancer patients. The high incidence of metastases of colorectal cancer to the liver is poorly understood. There are several ways to explain this high incidence. Two main hypotheses, those of Paget and Ewing, explain this high incidence by the “seed and soil” theory and the haemodynamic theory, respectively. The “seed and soil” theory postulates that only the appropriate “seed” will grow in the matching “soil” whereas the haemodynamic theory postulates that the anatomical orientation of an organ is the determinant of metastasis to occur. Animal experiments have shown that the theory of Ewing fits our model because colon cancer cells administered to the portal vein are all retained in the liver. This finding explains the high incidence of liver metastasis from colorectal cancer because this suggests that all cancer cells shed into the blood stream will be trapped in the liver and that arrest in the liver is a nonspecific event. However, the success of the development of a tumor at a secondary site is dependent on more factors than cell arrest. Extravasation and migration are considered to localize the cancer cell to a favourable site for proliferation. Our studies have shown that arrested cancer cells are not very mobile and do not need an extravasation step in order to start proliferation but initially proliferate intravascularly. Extravasation means that cancer cells leave the blood vessels and invade liver parenchyma, consequently being in contact with hepatocytes. In our model endothelial cells retract rapidly allowing direct contacts between cancer cells and hepatocytes. In the end, the result is the same but the mechanism is different. This indicates that extravasation of cancer cells is not essential for the formation of tumors in the liver.

The fact that different colon cancer cell lines have different capacities of forming tumors in the liver indicates that events after cell arrest play crucial roles as well. Organ-specific tumor growth can be dependent on a microenvironment matching the cancer cell allowing tumor development in that specific organ. A match between adhesion molecules expressed on cancer cells and ECM present in the target organ can allow development of a secondary tumor. However, it was also found that cancer cells rapidly undergo interactions with host tissue after initial cell arrest. These findings suggest that interactions between the “seed” and the “soil” are important for tumor development as well. It may well be that both hypotheses are valid to explain the high incidence of liver metastases from colorectal cancer. In our model, it means that cancer cells are retained due to the anatomical properties of the liver whereas only cancer cells that have the right properties in relation with host tissue (hepatocytes) are able to form tumors.
Another mechanism of tumor progression is considered to be expression of matrix metalloproteinases and in particular gelatinases. They have been correlated with stage of disease and animal models have shown inhibition of tumor growth when using both natural inhibitors of MMPs and synthetic inhibitors.

Detection of proteinases in tissue sections using dye-quenched (complete) substrates allows localization of proteolytic activity. Localization of gelatinolytic activity at the ECM of tumors was demonstrated on unfixed cryostat sections. This localization suggests a role of gelatinases in tissue remodelling and/or angiogenesis, but the (patho)physiological role in tumor progression remains speculative. Therefore, the effect of \textit{in vivo} MMP inhibition on the development of liver tumors was evaluated. Daily administration of a selective MMP inhibitor marginally reduced tumor volume. In contrast, the number of tumors that developed was increased by 2-fold. A possible explanation is that the host immune system is also affected by MMP inhibition. It has been suggested that the effects of MMP inhibitors in clinical trials have been disappointing so far, because patients with advanced cancer were included in these trials. Therefore, it was hypothesized that MMP inhibitors may be beneficial for early stage cancer patients or to prevent undetected metastases. However, our results do not support that hypothesis but show that even the opposite effect i.e. induction of tumors is a possibility. It is difficult to predict what the final outcome is of inhibition of MMPs in the treatment of cancer because it has become evident that MMPs are not simply “bulldozers” that destroy ECM but also have many functions which are not related with destruction of ECM. These functions can be protumorogenic and antitumorogenic and the sum of these actions will determine the outcome.