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### Pathophysiology of peritoneal carcinomatosis

The development of peritoneal metastases is a significant clinical issue frequently occurring with a variety of intraabdominal malignancies such as ovarian, gastric, pancreatic and, to a lesser extent, colorectal carcinomas, and is associated with a poor prognosis. Although there is growing evidence that intraperitoneal chemotherapy in certain patients may be of benefit in terms of disease progression and survival, the molecular mechanisms involved are poorly understood.

The development of peritoneal metastases appears to be a multistep process: resistance to anoikis, cancer cell dissemination from the primary tumour into the peritoneal cavity, adherence of the tumour cell to the peritoneal mesothelium prior to tumour cell invasion through into the extracellular matrix (ECM), proliferation and neovascularisation.

The mechanisms involved in these processes have been investigated. In particular several cell adhesion molecules have been implicated, for example, E-cadherin, which mediates cell-cell adhesion, has been observed to be down regulated especially in response to hypoxia in ovarian and colorectal cancer cell lines resulting in reduced homotypic adhesion and increased invasion. More recently *wwox* has been identified as a tumour suppressor gene and loss of its expression in ovarian epithelial cancers has been shown to reduce tumour cell adherence. The mediators of tumour cell adhesion to the peritoneum also have been the subject of numerous studies. All have shown that both cell-cell and cell-ECM interactions play a role and a number of cell surface molecules have been demonstrated to play a role including the  $\alpha_2$ ,  $\alpha_3$  and  $\beta_1$  integrin subunits, CD44 / hyaluronan interactions and intercellular adhesion molecule-1.

Cytokines and growth factors are also likely to mediate the development of peritoneal carcinomatosis. The peritoneum is a rich source of chemokines, cytokines and growth factors that have been implicated in the metastatic process such as IL-6, IL-8, FGF-2 and VEGF. Some of the processes described above appear to be modulated by proinflammatory cytokines, in particular IL-6 and TNF- $\alpha$ , both of which are markers of surgical trauma and this may explain why surgical trauma appears to influence tumour growth and local recurrence rates. The ascitic fluid seen in peritoneal disease has also been described as a metastatic milieu as it is rich in molecules that promote tumour growth and invasion. For example the chemokine CXCL12, which has recently been found to be secreted also by mesothelial cells, is found in high concentrations in peritoneal fluid and increases tumour cell migration. Other components such as proteases including MMPs and uPA also enhance tumour invasion.

Although the mechanisms involved in peritoneal dissemination have been partly elucidated, further work needs to be performed to fully understand the mediators of this process to enable the identification of new targets for the development of novel treatments such as the use of monoclonal therapies to improve the outcomes in these patients who currently have such a poor prognosis.