Molecular Biology of Peritoneal Carcinomatosis

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Introduction

Peritoneal carcinomatosis refers to the complex sequence of events by which tumour cells disseminate from their primary organ of origin to establish independent metastatic deposits on the visceral and parietal peritoneal lining of the abdominal cavity. With few exceptions, once peritoneal dissemination occurs the malignant process is deemed non-curative as it is seldom amenable to surgical resection and current chemotherapeutic regimens are merely palliative. An understanding of the molecular events involved in peritoneal carcinomatosis is therefore of paramount importance if we are to advance therapeutic strategies for this devastating form of cancer progression.

In order to better understand the events involved in peritoneal carcinomatosis it is necessary to break the process down into a series of steps known as the "peritoneal metastatic cascade". Although this subdivision is analytically useful, it is important to realise that each step in the metastatic cascade does not necessarily occur in isolation, but represents a continuous and interdependent process.

Firstly, individual or clumps of tumour cells must break free of the primary tumour mass and gain access to the peritoneal cavity. They are then free to disseminate around the peritoneal cavity, with their ultimate destination being determined by many factors, including gravity, the movement of the abdominal viscera, and the flow of ascitic fluid. The first surface that free tumour cells encounter is the innermost layer of the peritoneum, the mesothelium. The mesothelium forms a cellular monolayer supported by a basement membrane. Adherence of tumour cells to the mesothelium is the second step in the metastatic cascade, which temporarily arrests the tumour cells to their eventual site of metastasis. The third step involves the penetration of the mesothelial monolayer and its basement membrane giving tumour cells access to the submesothelial connective tissue. Invasion of the underlying connective tissue, the fourth step, provides the necessary scaffold for tumour proliferation, and provided tumour-stromal interaction is compatible results in the establishment of a discrete metastatic tumour deposit. The final step involves the induction of angiogenesis to sustain tumour proliferation and enable further metastatic growth.

The aim of this chapter is to sequentially review each step of the peritoneal metastatic cascade and to highlight the molecular mediators that may be involved.

Peritoneal Tumour Dissemination

Dissemination of tumour cells from the primary cancer may occur by one of several mechanisms. Probably the most important mechanism in gastrointestinal cancers is the spontaneous exfoliation of tumour cells from cancers that have invaded through the full thickness of the bowel wall and its investing serosa. This process may be aided by the down-regulation of intercellular adhesion molecules on the tumour cell surface [1].

It is well recognised that viable tumour cells can be isolated from ascitic fluid or by direct contact with the tumour at the time of surgery and their presence has been linked with poor prognosis [2,3]. In a similar manner, perforation of the primary cancer, which may either be spontaneous or occur inadvertently during surgery, increases the rate of local recurrence and reduces survival [4,5]. Alternatively, tumour cells may be inadvertently liberated from transected lymphatics and blood vessels during the course of surgical resection. Whatever the mechanism of spillage, once liberated from their normal tissue constraints, the tumour cells are free to be disseminated around the peritoneal cavity.

Mesothelial Adhesion

Adherence of liberated tumour cells to the mesothelium is the second step in the peritoneal metastatic cascade. Several candidate adhesions molecules have been implicated in this process, including the lymphocyte-homing molecule, CD44, members of the integrin superfamily, the Selectins, and a variety of other leukocyte associated adhesion molecules.

Much of the original work on tumour-mesothelial interactions was based on studies of peritoneal sepsis. Parallels were drawn between the mesothelial cell and the endothelial cell, in that both cell types form monolayers that regulate the passage of leukocytes between serosal cavities. The endothelial adhesion molecules involved in leukocyte trafficking have been well characterised, and a search for related molecules on mesothelium revealed an overlapping, yet distinct, pattern of expression. Mesothelial cells were shown to express adhesion molecules belonging to the Immunoglobulin Superfamily (Intercellular Adhesion Molecule-1 (ICAM-1), Vascular Adhesion Molecule-1 (VCAM-1), Platelet-Endothelial Cell Adhesion Molecule-1 (PECAM-1)) [6], the Selectin Family (Platelet (P) - and Endothelial (E) - Selectin) [7] and the lymphocyte-homing receptor, CD44 [8]. Whilst ICAM-1 and PECAM-1, are constitutively expressed by quiescent mesothelium, VCAM-1 and E-Selectin require mesothelial activation by pro-inflammatory cytokines (Il-1β, TNF-α, IFN-γ) to induce their expression. Meso-

thelial expression of these adhesion molecules has subsequently been shown to play an important part in lymphocyte trafficking during peritoneal inflammation and it is proposed that the same adhesion molecules may be "hijacked" by invading tumour cells. In this way, Alkhamesi et al. have shown that mesothelial ICAM-1 may be involved in tumour-mesothelial adhesion and its downregulation by exogenous heparin may have a beneficial effect [9].

Schlaeppi et al. studied the mechanisms involved in the adhesion of four colorectal cancer cell lines to mesothelial cell monolayers and to various extracellular matrix proteins [10]. All cell lines adhered rapidly to the mesothelial monolayer, but this adhesive event was not inhibited by either anti-integrin antibodies or antibodies against CD44. In contrast, cell adhesion to the extracellular matrix components was completely integrin-dependent, and could be inhibited by anti-β1 integrin antibodies. The authors concluded "initial colorectal tumour cell-mesothelial cell interaction occurs through an integrin-independent mechanism while adhesion to matrix proteins are integrin-dependent events."

Kotanagi et al. studied the growth of colorectal cancer cells in the peritoneal cavity of mice [11]. They established two cancer cell lines from a patient with colon cancer: AKT-CC-K-LM cells from liver metastatic nodules and AKT-CC-K-PC cells from peritoneal nodules. They found that the two cell lines differed in their morphology in vitro, and in their expression of cell surface adhesion molecules. The expression of carcinoembryonic antigen (CEA), E-cadherin and sialyl-Lewis antigens was significantly higher in AKT-CC-K-LM cells. The expression of CD44v6 was significantly higher in AKT-CC-K-PC cells. After injection of AKT-CC-K-LM cells into the spleen or peritoneal cavity of mice, metastatic nodules were observed only in the liver. In contrast, the injection of AKT-CC-K-PC cells into the spleen or peritoneal cavity yielded metastatic nodules only in the peritoneal cavity. Thus, contrary to the findings of Schlaeppi [10], these authors suggested that the adhesion molecule CD44 was involved in tumour-peritoneal adhesion and might account for the site-specific nature of peritoneal tumour metastasis.

Similar evidence for the involvement of CD44 in tumour adhesion to the peritoneum has been found in models of ovarian and gastric cancer models [11,12]. Cannistra et al. studied the expression of adhesion molecules on ovarian cancer cells and their role in tumour-mesothelial adherence [13]. They showed that both ovarian cell lines and fresh ovarian cancer specimens exhibited CD44 expression. Tumour-mesothelial adhesion was partly inhibited by anti-CD44 antibodies. Similar studies, by the same authors, have subsequently identified a role for the β1-integrins in ovarian-mesothelial adhesion. They have demonstrated an additive inhibitory effect when β1-integrin blocking antibodies are combined with anti-CD44 antibodies in tumour-mesothelial adhesion studies. The inhibitory effect of anti-β1 antibody was attributed to the disruption of tumour β1-integrin interactions with its ligand, fibronectin, on the mesothelial cell surface. A similar inhibitory effect could be reproduced with the use of anti-fibronectin blocking antibodies or the peptidomimetic RGD molecules, which competitively block integrin-fibronectin interactions.

Other leukocyte associated adhesion molecules that have been implicated in peritoneal tumour metastasis include the Very Late Antigens (VLA-2 and VLA-3) and the Leukocyte Functioning Antigen (LFA-3). Mayer et al. performed a histological study to examine the expression of leukocyte cell adhesion molecules in gastric cancer [14]. They found that both primary tumours and lymph node metastases expressed LFA-3. Positive LFA-3 expression was associated with a poorer outcome and correlated with vessel invasion, tumour recurrence and decreased survival time.

Mesothelial Invasion

Before invading tumour cells can gain firm adherence to the submesothelial connective tissue, they must penetrate the mesothelial monolayer. Two possible mechanisms exist: either tumour cells invade the intercellular spaces between adjacent mesothelial cells; or they must destroy the mesothelial monolayer.

Akedo et al. observed three patterns of tumour growth when rat ascites hepatoma cells where co-cultured with mesothelial monolayers [15]. Tumour cells either formed "piled-up" nests upon the mesothelial monolayer, exhibited invasive growth between adjacent mesothelial cells, or failed to attach and grew in suspension. The implication was that intercellular invasion was the predominant mechanism for tumour-mesothelial invasion.

However, other researchers have commented on a change in mesothelial morphology that occurs in areas of tumour cell invasion [16,17]. Mesothelial cells take up a characteristic "rounded" morphology with separation of cell-cell contacts to expose the submesothelial basement membrane. Yonemura et al. explored this observation further using a mouse model and the gastric cell line, MKN-45-P [18]. Intraperitoneal inoculation of MKN-45-P resulted in mesothelial contraction and eventual exfoliation. Similar effects could be induced in vivo by intra-peritoneal injection of IL-6, TNF-α and IL-8, and in-vitro by cytokine stimulation of mesothelial monolayers. It was postulated that tumour-derived cytokines were responsible for disruption of the mesothelial barrier, exposing the submesothelial basement membrane, and facilitating tumour adhesion.

The author's research would favour mesothelial destruction to be the predominant mechanism underlying tumour-mesothelial invasion. Using a threedimensional in vitro model of the human peritoneum [19], it was found that colorectal cancer cell lines adhered rapidly to the outer mesothelial monolayer. Whilst the majority of adherent cells showed proliferative growth on the mesothelial surface without invasion, a proportion invaded between adjacent mesothelial cells. Closer inspection revealed that invasion of the mesothelium was frequently accompanied by changes in mesothelial cell morphology in keeping with apoptosis, namely membrane blebbing, cell shrinkage, and nuclear fragmentation (Fig. 1).

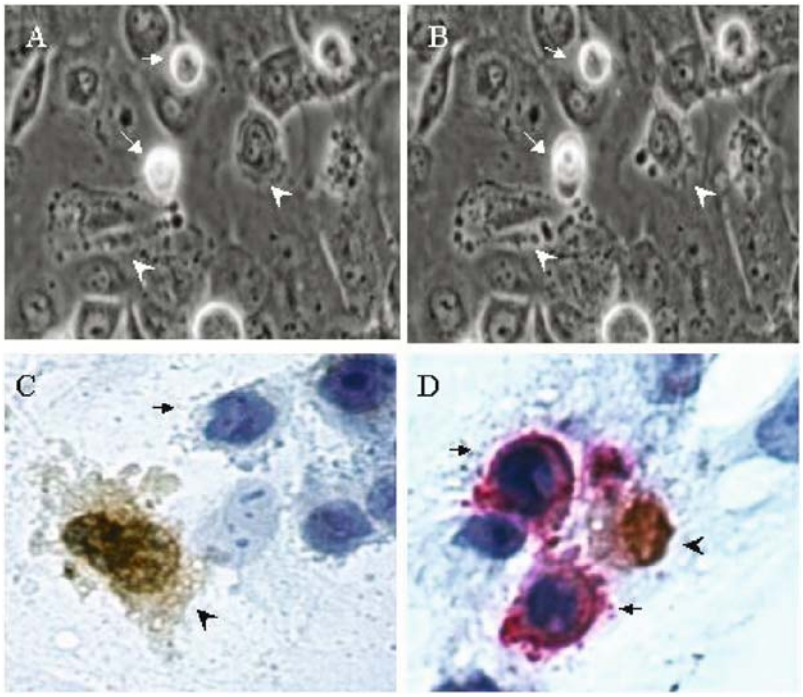

Figure 1. Mesothelial-SW480 co-cultures. A and B: Phase contrast photomicrographs illustrating the cellular changes of apoptosis (membrane blebbing, cell shrinkage, and nuclear fragmentation) observed in mesothelial cells (arrowheads) adjacent to adherent SW480 tumour cells (arrows). Original magnification x200. C and D: Immunocytochemistry of mesothelial-SW480 co-cultures. Mesothelial cells (arrowheads) adjacent to SW480 tumour cells (arrows) show apoptotic changes with characteristic nuclear fragmentation. Original magnification x200. Reproduced with permission from Ann Acad Med Singapore 2003;32:219-225

The presence of mesothelial apoptosis upon co-culture with colorectal cancer cell lines was confirmed by DNA fragmentation assays and immunocytochemistry.

In an attempt to explore the molecular mediators involved in tumour-induced mesothelial apoptosis the potential role of the Fas/FasL apoptotic death signalling was investigated [20]. Human mesothelial cells and SW480 colorectal tumour cells constitutively expressed Fas and FasL mRNA and protein as determined by RT-PCR and confocal fluorescent microscopy. Stimulation of human mesothelial cells with anti-Fas mAb or crosslinked sFasL induced apoptosis, confirming the functional status of the Fas receptor. Pretreatment of SW480 cells with a blocking recombinant anti-FasL monoclonal antibody significantly reduced mesothelial apoptosis (Fig. 2). Thus it would appear that tumour-induced mesothelial apoptosis may, at least in part, be mediated via a Fas-dependent mechanism. These

finding require further investigation in animal models as well investigation of other apoptotic mediators such as TRAIL receptor signalling.

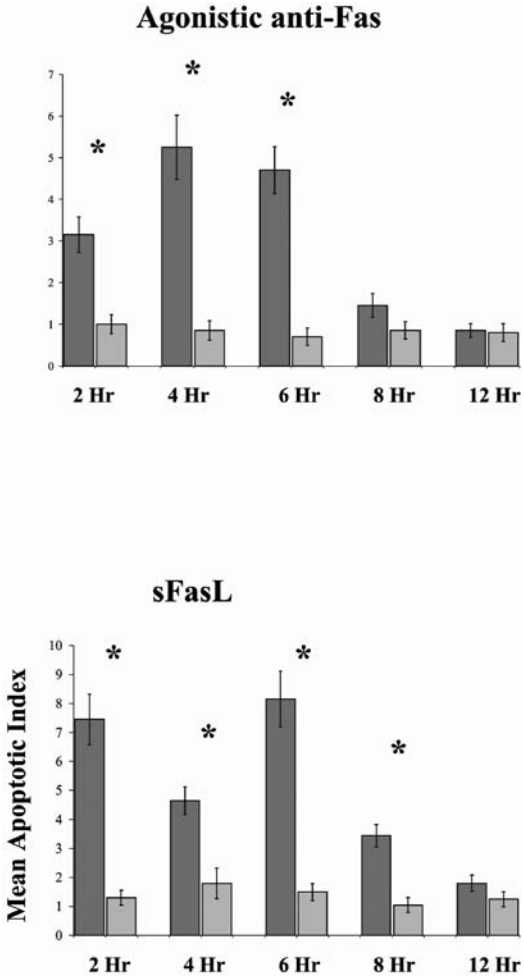

Figure 2. Assessment of the functionality of human mesothelial Fas. Mesothelial monolayers were incubated with an agonistic anti-Fas mAb or stimulating crosslinked sFasL (dark columns). Controls were untreated mesothelial monolayers (light columns). Mesothelial apoptosis was detected using a TUNEL assay. Results are expressed as mean apoptotic index of triplicate experiments ± SD. * $P < 0.05$, Mann-Whitney U Test. Reproduced with permission from Br J Cancer 2004;90(7):1437-1442

Stromal Invasion and Proliferation

Having attached to the peritoneum and penetrated the mesothelial barrier, tumour cells must next gain stable adherence to the submesothelial connective tissue before they can invade and proliferate.

Current evidence suggests that adherence to the submesothelial connective tissue is orchestrated via integrin-ligand interactions. Schlaeppi et al. found that adhesion of colorectal cell lines to extracellular matrix components was completely integrin dependent [10]. These findings are supported by the work of Yonemura et al. [21] who used a gastric cell line, MKN-45, to establish a highly metastatic variant, MKN-45-P, by serial peritoneal passages in a mouse model. The differential expression of various metastasis-related genes (integrin subunits, motility factors, proteases, growth factors) between MKN-45 and MKN-45-P were examined by RT-PCR. Integrin $\alpha 2$ and $\alpha 3$ subunits were significantly elevated in MKN-45-P compared to MKN-45. These α-integrins dimerise with $\beta 1$-subunits to form adhesion molecules for various basement membrane proteins, including fibronectin, laminin, and collagen IV, which are secreted by human mesothelium [71]. Treatment with anti-$\beta 1$-integrin antibodies significantly inhibited the adherence of MKN-45-P in an ex-vivo peritoneal model, suggesting a role for $\beta 1$-mediated integrin adhesion to the submesothelial basement membrane.

Thus it would appear that integrin mediated adherence is involved in stabilisation of invading tumour cells to the submesothelial connective tissue. Activation of tumour integrin receptors would also serve to facilitate tumour proliferation and motility through well established $\beta 1$ integrin-mediated cell signalling pathways.

Further proliferation and survival of the adherent tumour cells requires a compatible interaction between the invading cells and the peritoneal stroma. Although the consequences of tumour-stromal interaction have been much studied in other metastatic systems, this interaction has received little attention with respect to peritoneal metastasis development.

Davies et al. showed that epidermal growth factor (EGF) enhanced the invasive potential of mammary carcinoma cells when injected into the peritoneal cavities of rats [22] and that this growth promoting effect was due to the production of EGF by the peritoneal host tissue. Injection of a murine mammary carcinoma cell line, which was negative for EGF production, resulted in the production of multiple small peritoneal deposits, which could be abolished by simultaneous injection of anti-EGF antibodies. No such effect was seen with subcutaneous tumour growth, suggesting a site-specific requirement for EGF in peritoneal metastases.

Using an in vitro Transwell system, van der Wal et al. found that mesothelial cells inhibited the growth of CC531 colon carcinoma cells, whilst CC531 cells stimulated mesothelial cell growth [23]. Both cell types produced insulin growth factor-1 (IGF-1), and possessed IGF-receptors. In co-culture, IGF-1 potentiates the inhibitory effect of mesothelial cells on CC531 proliferation, whilst enhancing mesothelial proliferation. It was postulated that the inhibitory effects of IGF-1 like molecules might explain why tumour cells grow poorly in a surgically uncompromised abdomen.

The role of chemokines in the development of peritoneal carcinomatosis was studied in a murine model of peritoneal carcinomatosis by Yasumoto et al. [24]. They found that the CXCL12 chemokine enhanced proliferation of the NUGC4 gastric tumour cell line and that specific inhibition of its receptor, CXCR4, effectively reduced tumour growth and ascites formation. CXCR4 expression in primary gastric cancers also significantly correlated with the clinical development of peritoneal disease.

Said et al. have shown the importance of the extracellular glycoprotein SPARC (secreted protein acidic and rich in cysteine) in a murine model of ovarian peritoneal carcinomatosis [25]. Compared to wild-type mice, SPARC-null mice were found to have significantly shorter survival and more extensive nodular peritoneal dissemination when inoculated with a syngeneic ovarian cancer cell line. Immunohistochemical analysis of tumour nodules from SPARC-null mice revealed higher proliferation and lower apoptotic indices.

The author has previously been interested in the potential role of the heparin-binding growth factors (HBGF's) in stimulating peritoneal carcinomatosis. This diverse group of growth factors, which includes vascular endothelial growth factor (VEGF), heparin-binding epidermal growth factor (HB-EGF), basic fibroblast growth factor (bFGF), platelet derived growth factor (PDGF), and interleukin-8 (IL-8), shares the common ability to bind exogenous heparin-derived molecules. This heparin binding capacity enhances growth factor – ligand interaction.

HBGF's are involved in normal wound healing, where their expression is upregulated by the early inflammatory cytokines IL-1β and TNF-α, which are also produced by peritoneal mesothelial cells in response to injury or surgical trauma. In healing wounds HBGF's stimulate fibroblast and epithelial proliferation, and due to their additional angiogenic properties also probably contribute to wound vascularisation. Using in vitro human mesothelial monolayers, it was shown that peritoneal mesothelial cells constitutively expressed bFGF, HB-EGF and two spliced variants of VEGF ($VEGF_{121}$ and $VEGF_{165}$) [26]. Stimulation with exogenous IL-1β and TNF-α upregulated mesothelial production of HB-EGF and VEGF, whereas IL-6 had no detectable effect, and IL-2 suppressed mesothelial HB-EGF and bFGF. Many gastrointestinal cancers are known to express receptors and to be responsive to the HBGF's. In addition to stimulating tumour cell proliferation, HBGF's upregulate tumour expression of the integrin and immunoglobulin superfamily of adhesion molecules. Thus the production of HBGF's by the activated peritoneum may facilitate tumour cell adhesion, proliferation and invasion. The significance of this finding lies in the ability to inhibit the actions of HBGF's with exogenous heparin-like molecules and therefore suppress peritoneal metastasis deveolment [9].

Assuming tumour cells successfully attach to the submesothelial connective tissue and have encountered a favourable host response, it is then necessary for them to invade the extracellular matrix. The matrix metalloproteinases (MMPs) may play a central role in stromal invasion. Yonemura et al. studied the role of MMP-7 in a mouse model of peritoneal carcinomatosis [27]. Specific antisense oligonucleotides inhibited the expression of MMP-7 by the highly metastatic gastric cell line, MKN-45-P, and suppressed invasion without altering cell proliferation. In

addition, survival of MKN-45-P bearing mice, which had been pre-treated with antisense oligonucleotides, was significantly better than that of control mice. Aparicio et al. found that the MMP inhibitor, batimastat, significantly reduced metastasis formation and prolonged survival in a rat model of peritoneal carcinomatosis [28]. However, batimastat treatment was associated with marked peritoneal inflammation and ascites, raising concerns about its potential as an anti-metastatic agent in humans.

Other potential mediators of peritoneal stromal invasion include the urokinase-plasminogen activating (UPA) system. UPA has been widely implicated in many cancer systems. In our laboratory, we have shown that tumour expression of the UPA receptor (UPAR) and its ligand is upregulated in vitro by inflammatory cytokines or postoperative peritoneal drain fluid, suggesting enhanced activation of this system in the early postoperative period. Pre-treatment of colorectal tumour cells with anti-UPAR antibody significantly reduced invasion in a Matrigel invasion assay (Fig. 3).

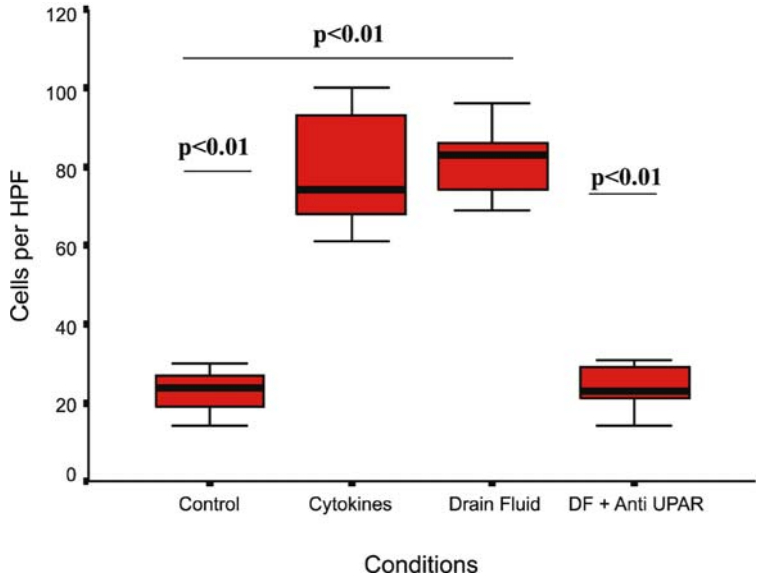

Figure 3. Incubation of HT29 colon cancer cell lines with physiological doses of TNF-α or 20% v/v postoperative drain fluid significantly increased cellular invasion in a Matrigel invasion assay. Pre-treatment of HT-29 cells with anti-UPAR antibody inhibited drain fluid induced cellular invasion. Control experiments used HT-29 cells with neither cytokine, drain fluid, nor anti-UPAR treatment

Furthermore, the urokinase receptor is known to interact with $\alpha_v\beta_5$ integrin, a receptor for the extracellular matrix protein vitronectin, leading to enhanced tumour cell migration and invasion [29]. The protease inhibitor Bikunin (bik) inhibits tumour cell invasion and metastasis through suppression of UPA mRNA

expression. Tansfection of the human ovarian carcinoma cell line HRA with a vector harbouring a cDNA encoding for bik resulted in reduced invasion, but not proliferation, adhesion, or migration relative to the parenteral cells [30]. Inoculation of bik (+) clones into animal models resulted in reduced peritoneal dissemination and long term survival.

Tumour-Peritoneal Angiogenesis

As the peritoneal metastatic deposit grows it needs to develop a blood supply to meet its increasing metabolic demands. The deeper layer of the peritoneum contains a rich capillary network and is ideally suited to this function. Surprisingly little is known about the mediators of peritoneal angiogenesis. The potential role of HBGF's in tumour-stromal interactions has been described and it should be recognised that many of these growth factors, which include VEGF and IL-8, also possess angiogenic properties. Fan et al. showed that the angiogenesis inhibitor, TNP-470, reduced growth and dissemination of a colorectal cancer cell line in a nude mouse model compared to sham treated animals [31]. Furthermore, the mean survival time was significantly longer in the TNP-470 treated group.

Suganuma et al. investigated the role of the renin-angiotensin system in peritoneal carcinomatosis from ovarian cancer [32]. The angiotensin II type I receptor (AT1R) was highly expressed in malignant ovarian adenocarcinomas and its expression showed a positive correlation with VEGF and microvessel density. In a mouse model of ovarian peritoneal carcinomatosis, the administration of the AT1R blocker, candesartan, resulted in the reduction of peritoneal dissemination, decreased ascitic VEGF concentration, and suppression of tumour angiogenesis. Stoeltzing et al. used a human colon cancer cell line transfected with a vector containing angiopoietin-1 in a mice model of peritoneal carcinomatosis [33]. Thirty days following tumour cell inoculation, a significant reduction in the number of peritoneal metastases, tumour volume, vessel counts, and tumour cell proliferation were observed in the animals inoculated with angiopoietin-1 over-expressing tumours as compared to control animals. Other animal studies utilising adenoviral vector mediated anti-angiogenic therapy have shown similar results with down-regulation of ascites formation, tumour growth, vascularity, and prolonged animal survival, underlining the importance of angiogenesis in the peritoneal metastatic cascade [34].

Summary

Peritoneal carcinomatosis can be thought of as a sequence of events that together form a peritoneal metastatic cascade. Presently our understanding of the molecular mediators that orchestrate this cascade is ill-understood. Initial tumour-mesothelial interaction appears to involve several adhesion molecules, including CD44, the

Selectins, and various leukocyte associated antigens. The exact molecules involved are probably determined by the nature of the metastatic tumour cell. Invasion of the mesothelial monolayer appears to occur by tumour-induced mesothelial apoptosis, at least in part via the Fas/FasL system, although invasion between intercellular spaces may also play a role. Adhesion to the submesothelial connective tissue is mediated by tumour integrin binding. The peritoneal stromal tissue appears to be a favourable host for tumour proliferation, providing a rich source of growth factors and chemokines known to be involved in tumour metastasis. Angiogenesis is vital to peritoneal tumour growth and although the peritoneum has a well developed blood supply the angiogenic events specific to peritoneal tumour metastasis remain to be elucidated. Further investigation is required to unravel the complexities of the peritoneal metastatic cascade and this will inevitably open up many avenues for novel therapeutic manipulation and disease modulation.

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