Review

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# Pathophysiology of peritoneal colorectal metastases

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## ABSTRACT

Colorectal cancer (CRC) disseminates through three routes; the lymphatic, the haematogenous, and the transcoelomic, which leads to the development of peritoneal carcinomatosis (PC). PC is associated with a poor prognosis and bad quality of life. A loco-regional treatment strategy for PC combining cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) has demonstrated promising clinical results. The comprehension of the molecular events of peritoneal disease spread is of the utmost importance for many reasons. The emergence of PC is the result of a molecular crosstalk between cancer cells and host elements, involving several well-defined steps together known as the peritoneal metastatic cascade. Individual or clumps of tumour cells detach from the primary tumour, gain access to the peritoneal cavity and become susceptible to the regular peritoneal transport. They attach to the distant peritoneum, subsequently invade the subperitoneal space, where angiogenesis sustains proliferation and enables further metastatic growth. These molecular events make up a continuous and interdependent process. The present publication reviews the current data regarding the molecular mechanisms underlying the development of colorectal PC, with a special focus on the peritoneum.

**Key Words:** *Colorectal cancer; peritoneal carcinomatosis; pathophysiology; peritoneal metastatic cascade*

## INTRODUCTION

Colorectal cancer (CRC) is the third most frequent cancer and the fourth most common cause of cancer related death worldwide [1,2]. Colorectal cancer disseminated through the lymphatic and haematogenous routes develop metastatic disease to remote sites such as the liver, lung, bones, brain, etc. Furthermore, CRC may give rise to transceolomic spread of tumour cells in the peritoneal cavity, which eventually leads to the development of peritoneal carcinomatosis (PC) [3].

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The precise incidence of PC is not known, either because the pre-operative imaging techniques (CT, MRI, PET, PET/CT) are of low sensitivity, or because there is heterogeneity among published methods and findings [4,5]. It has been reported that the presence of PC at initial diagnosis (synchronous PC) varied from 4.3% [6] to 8% [7], in contrast to recurrence that varied from 4% [6] to 5% [7].

In the past PC was considered an incurable condition and only systemic palliative chemotherapy was administered to patients with poor results [8]. Cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) has shown promising clinical results in the treatment of PC of CRC origin. The purpose of CRS is the resection of the entire macroscopically visible tumour using the standard peritonectomy procedures while the purpose of HIPEC is the eradication of the microscopic residual tumour [9,10]. Phase II and III studies have shown encouraging results using CRS and HIPEC in CRC patients with PC [11-13].

The manuscript attempts to describe the pathophysiology of PC data taking into consideration the underlying molecular mechanisms.

## THE PERITONEUM

The peritoneum is a continuous thin serous membrane covering the abdominal wall and the viscera. It is composed of a monolayer of mesothelial cells supported by a basement membrane that rests on a layer of connective tissue which is known as submesothelium (Figure 1). The mesothelium is a monolayer of flattened, stretched, squamous-like or cuboidal mesothelial cells. The cuboidal cells are found in the liver, the spleen, the milky spots of the omentum, and the peritoneal side of the diaphragm overlying the lymphatic lacunae [14,15]. They are also found after injury to the mesothelium. Squamous-like mesothelial cells contain few mitochondria, a poorly developed Golgi apparatus and little rough endoplasmic reticulum (RER), which are located centrally near the round or oval nucleus [16]. Cuboidal mesothelial cells contain a central prominent nucleolus, abundant mitochondria and RER, a well-developed Golgi apparatus, microtubules and microfilaments [17]. The luminal surface of mesothelial cells has numerous microvilli varying in shape, size and density that increase the functional mesothelial surface area [18]. Cilia have been identified on the surface of resting mesothelial cells [19]. The mesothelium is a dynamic layer contributing substantially to the structural, functional, and homeostatic properties of the peritoneum [16]. The basement membrane is a thin laminar network containing type I and IV collagen, proteoglycans and glycoproteins. It acts as a selective barrier to macromolecules which enter into the submesothelial layer [16]. The submesothelium is a complex network of extracellular matrix (ECM) consisting of different types of collagen, glycoproteins, glycosaminoglycans and proteoglycans. Blood vessels, lymphatics, and various cell types (fibroblasts, resident tissue macrophages, and mast cells) also reside in this layer [16,20]. The peritoneum facilitates the transport of fluid and cells across the serosal cavities [21]. The microvilli on the luminal surface of the mesothelial cells play an important role in this process by increasing the surface area and binding fluids in their glycosaminoglycan-rich glycocalyx thereby aiding absorption [22]. Furthermore, it provides a slippery and non-adhesive surface that allows intracoelomic movements [23]. This slippery and non-adhesive surface is established by the secretion of a small amount of sterile fluid that contains phosphatidylcholine produced by each mesothelial cell. In addition, it acts as a first line of defense in host resistance [24]. A last function is the release of growth factors that are involved in tissue repair [25]. As a consequence the peritoneum must be considered an organ with a structural and protective function for the contents of the abdominal cavity [20,26,27].

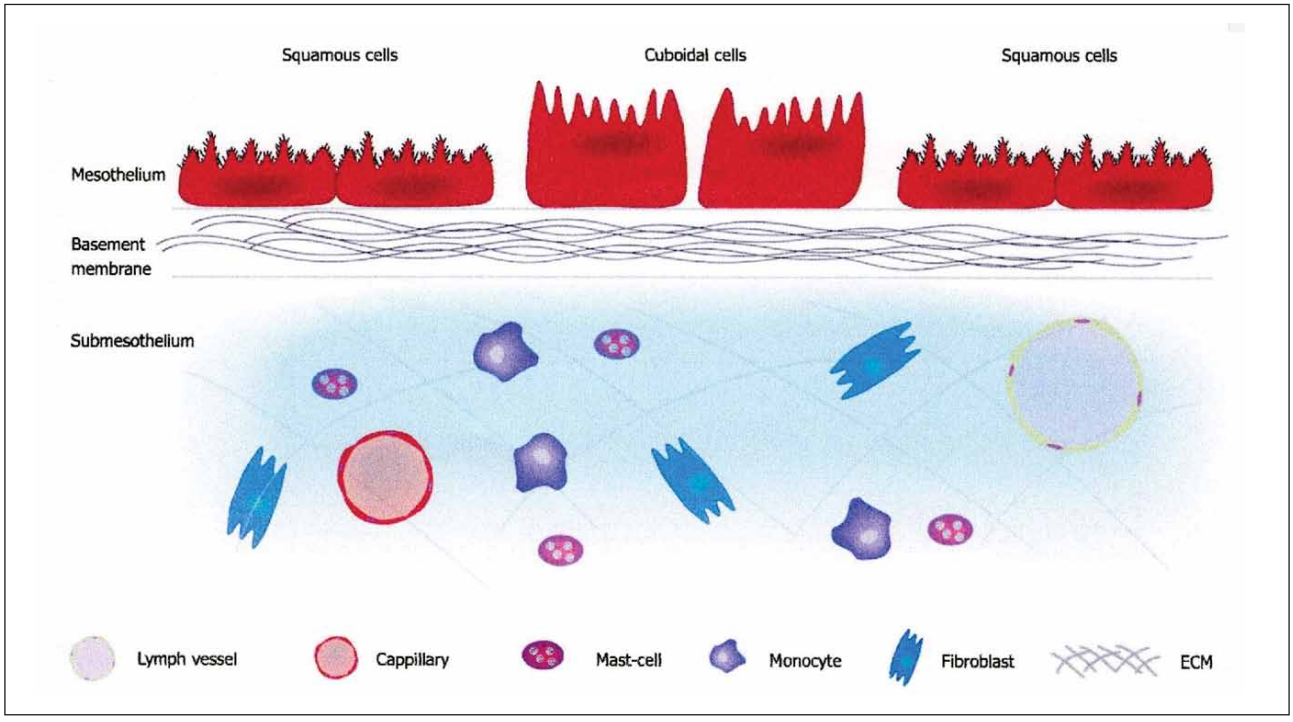


**FIGURE 1.** Structure of the peritoneum.

## EMERGENCE OF PC

### The following are listed in Table 1.

PC is the result of a molecular cross-talk between tumour cells and host elements and a well-defined multi-step process. Cancer emboli or isolated tumour cells gain access to the peritoneal cavity detached from the tumour itself. These free tumour cells follow the peritoneal transport routes before their attachment to the distant peritoneum where they invade the submesothelial space and find in the underlying connective tissue the proper space for proliferation with angiogenesis which enables the metastatic growth [28]. This process is known as the "peritoneal metastatic cascade" which does not occur in isolation but in fact it is a continuous and interdependent process (Figure 2) [28].

### Pre-operative spontaneous development of PC

The tumour cells are detached as a result of spontaneous exfoliation from a tumour which has invaded the entire thickness of the wall of the organ of origin and has already disrupted the serosa [29]. Intracellular adhesion molecules on the tumour cell surfaces are down-regulated promoting the exfoliation of the cancer cells. E-cadherin is one of the adhesion molecules that belongs to the type I subfamily of cadherins [30,31]. E-cadherin binds homotypically with E-cadherin of neighbouring cells through its $Ca^{+2}$-dependent extracellular domain. The cytoplasmic tail of E-cadherin associates with p120, α-, β-, and γ-catenin, which is responsible for the connection with the actin cytoskeleton and allows in- and out-signal transduction [30-33]. The down-regulation of E-cadherin has been confirmed to be associated with dedifferentiation, progression, and metastasis of CRC [34,35]. It has also been established that down-regulation of E-cadherin occurs for gastric [36,37], and ovarian cancer with PC [38,39]. Reduction of cell-cell adherence, by the loss of E-cadherin, and the upregulation of mesenchymal N (neural) cadherin are the most important signs of the epithelial to mesenchymal transition (EMT). This process allows cells to separate, lose their apico-basal polarity, demonstrate heightened resistance to apoptosis, and revert to a more motile mesenchymal phenotype [40]. This is believed to play a crucial role in invasion and metastasis [33-41]. The overexpression of the epithelial polycystins PC1 and PC2 in a human colon carcinoma cell line is able to induce EMT-related alteration in E-cadherin, N-cadherin, Snail, and Twist mRNA expression. PC2 exogenous expression was found to increase cell migration [42]. PC1 and PC2 are membrane-spanning proteins. PC1 is a mechanosensor with G-protein coupled receptor properties that perceives

**TABLE 1.** Peritoneal metastatic cascade-molecular pathways.

| Peritoneal metastatic cascade | Molecules/molecular path ways |
|---|---|
| ***Exfoliation from the tumour*** | Spontaneous cancer cell shedding<br>E-cadherin<br>N-cadherin<br>EMT<br>PC1 and PC2<br>Interstitial fluid pressure<br>Intraoperative cancer seeding |
| ***Peritoneal transport*** | Mucinous ascites<br>Actin microfilament system<br>Lamellipodia, filopodia |
| ***Attachment to distant peritoneum*** | Trans-mesothelial dissemination<br>ICAM-1, PECAM-1, VCAM-1<br>TNF-a, IL-1b, IFN-γ<br>β1 integrin subunit<br>CD43, CD44<br>Hyaluronan<br>Translymphatic dissemination<br>Lymphatic stomata<br>Milky spots |
| ***Invasion in the subperitoneal space*** | Mesothelial cells rounding<br>HGF/SF<br>c-Met<br>Destruction of the mesothelial monolayer<br>Tumour-induced apoptosis<br>Fas ligand/Fas<br>Adherence to the basement membrane<br>Integrines<br>Peritoneal-blood barrier invasion<br>MMP-1, MMP-2, MMP-7, MMP-9, MM-P13, MMP-14<br>TIMP-1, TIMP-2, TIMP-3, TIMP-4<br>uPA/uPAR<br>plasminogen activator inhibitor-1 and -2 |
| ***Proliferation and angiogenesis*** | Proliferation<br>EGFR, EGF, TGFα<br>IGF-1, IGF- Binding Protein-3<br>Angiogenesis<br>HIF-1α , HIF-1β |

Explanations: E-cadherin=epithelial cadherin, N-cadherin=neural cadherin, EMT=epithelial to mesenchyme transition, PC=polycystin, ICAM=intercellular adhesion molecule, PECAM=platelet endothelial adhesion molecule, VCAM=vascular adhesion molecule, TNF=tumour necrosis factor, IL=interleukin, INF=interferon, CD43=sialophorin, HGF=hepatocyte growth factor, SF=scatter factor, MMP=matrix metalloproteinases, TIMP=tissue inhibitor metalloproteinases, uPA=urokinase plasminogen activator, uPAR=urokinase plasminogen activator receptor, EGFR=epidermal growth factor receptor, EGF=epidermal growth factor, TGF=tumour growth factor, IGH=insulin-like growth factor, HIF=hypoxia inducible factor, VEGF=vascular endothelial growth factor, VEGFR=vascular endothelial factor receptor

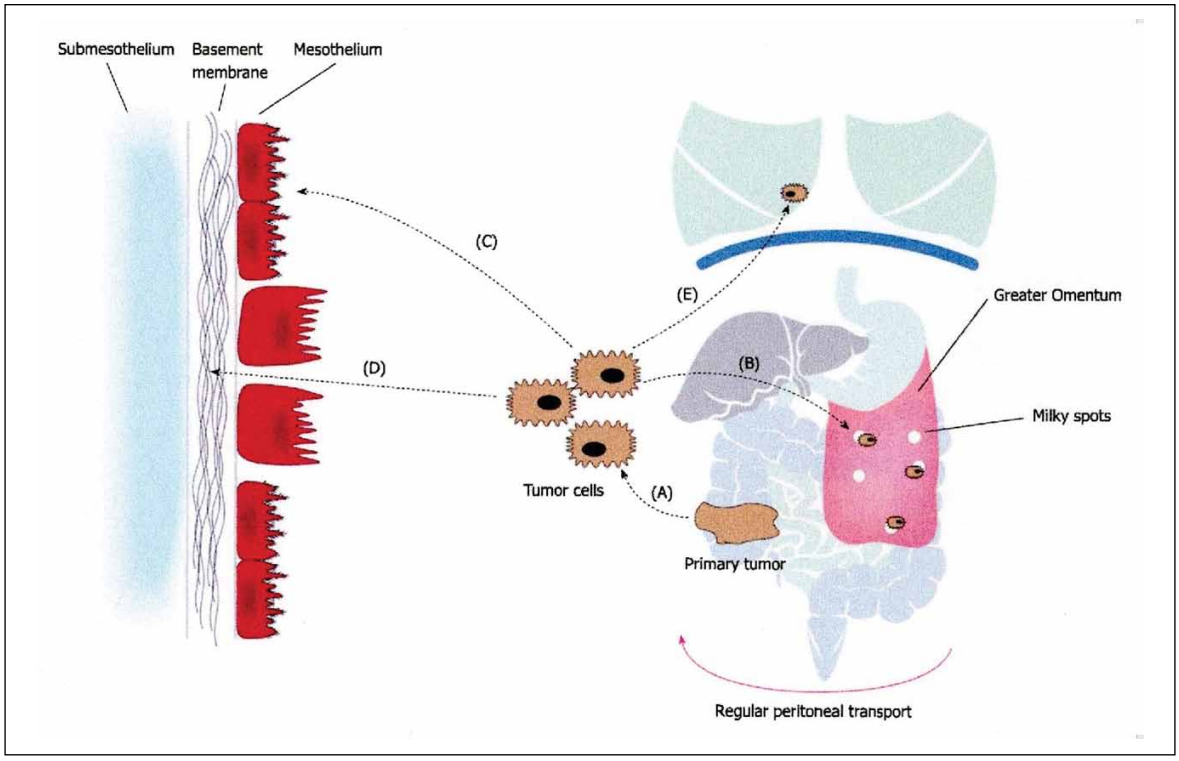


**FIGURE 2.** The peritoneal metastatic cascade.

extracellular mechanical signals and translates them into biochemical responses [43]. PC2 is a mechanosensitive $Ca^{+2}$ channel [44]. Both receptors interact through their C-terminal and form heterodimeric complexes at the cell membrane and at the primary cilia [45].

Spontaneous tumour cell exfoliation may also be the result of increased interstitial fluid pressure. It has been identified that the pressure in the tumour is important for the number of the exfoliated cancer cells and the size of cancer emboli invading the lymphatics around the primary tumour [46]. Interstitial hypertension may be the result of high osmotic pressure, increased vessel permeability and hyperperfusion, rapid cell proliferation, lack of effective lymphatic drainage, hyperplasia around blood vessels and increased production of ECM components [47].

### Intra-operative iatrogenic development of PC

Furthermore, free cancer cells may be found in the peritoneal cavity because of iatrogenic trauma. This may happen when the surgeon attempts to resect a malignant tumour located in narrow limits of resection such as the pelvis, or the head of the pancreas, or the gastro-esophageal junction, etc. Free cancer cells originate from traumatized interstitial tissues, or from transection of the relevant lymphatic network, or from venous blood loss [48].

## PERITONEAL TRANSPORT OF FREE CANCER CELLS

The direction and the final destination of free cancer cells depend on the anatomic location of the primary tumour and the continued cephalic circulation responsible for the clearance of fluid from the peritoneal cavity [49,50]. Changes in intra-abdominal pressure occur because of respiration, gravity, and intestinal motility. The peritoneal fluid circulation is a clockwise flow from the pelvis to the right paracolic gutter, to the subdiaphragmatic space, and finally to the pelvis again [27,51]. As a consequence, the subphrenic region, the lesser sac, the mesentery, the diaphragm, and the paracolic gutters, have an increased probability to accept cancer emboli that are expected to form peritoneal metastases [52]. The excreted mucus from mucinous adenocarcinomas appears to facilitate the intraperitoneal cancer distribution [51]. Other factors that influence peritoneal transport are the presence of adhesions and the entrapment of cancer cells in fibrin following surgical trauma. During the EMT malignant cells gain migratory and invasive properties involving the activity of the actin microfilament system resulting in the formation of actin-rich membrane protrusions: lamellipodia and filopodia. This is stimulated by pathological expression of growth factors, their receptors and signalling intermediates, which are the products of proto-oncogenes [53,54].

## ATTACHMENT TO THE DISTANT PERITONEUM

Additionally, the final destination of the free peritoneal cancer cells depends on the physical and biological properties of the tissue that will harbor them. The attachment of the free cancer cells may occur via two processes; the trans-mesothelial and the trans-lymphatic metastasis.

### Trans-mesothelial dissemination

During trans-mesothelial dissemination free tumour cells adhere directly to the distant mesothelium which is the innermost layer of the peritoneum. Mesothelial cells express adhesion molecules that belong to the immunoglobulin superfamily: intercellular adhesion molecule-1 (ICAM-1), platelet-endothelial cell adhesion molecule-1 (PECAM-1) and vascular adhesion molecule-1 (VCAM-1) [55]. Pro-inflammatory cytokines released following surgery or secreted by circulating tumour cells (tumour necrosis factor-α, IL-1β, IL-6 and interferon-γ) prepare a beneficial environment for the tumour-mesothelial interactions [56]. These cytokines enhance the expression of the adhesion molecules, ICAM-1 and VCAM-1, on mesothelial cells and induce the contraction of mesothelial cells, thereby exposing the basement membrane. In areas of absent or rounded mesothelial cells, the interaction between the tumour cells and the laminar network of the basement membrane is mediated through the β1 integrin subunit [57]. Tumour-mesothelial adhesion has been demonstrated by an interaction between mesothelial ICAM-1 and tumour expressed CD43 (sialophorin) [58]. The mesothelial cells secrete hyaluronan that wraps around the cell as a coat, protecting the mesothelium from vital infections and the cytotoxic effects of the lymphocytes. Hyaluronan is also involved in tumour-mesothelial adhesion through the interaction with tumour expressed CD44 [16,59,60]. CD44 is a cell surface glycoprotein which is widely expressed in neoplastic and non-neoplastic cells and is involved in migration of cells, homotypic and heterotypic cell-cell adhesion. The CD44 gene is composed of 20 exons, 10 of which are variably expressed [61]. The standard form is CD44s. Alternative splicing of 10 variant exons, which account for sequences located in the extracellular part of the CD44, results in the expression of CD44v1 up to CD44v10 [62]. The variant isoforms CD44v3 and CD44v6 are believed to play a role in the metastatic cascade of CRC. Expression of CD44v6 is largely restricted to the advanced stages (T3/T4) of CRC and is higher in metastatic cancer than in non-metastatic cancer [63]. It has been reported that high expression of CD44v6 is an independent poor prognostic factor for disease-free survival and overall survival [64].

### Trans-lymphatic dissemination

During trans-lymphatic dissemination the free cancer cells gain access to the submesothelial lymphatics through openings at the junction of two or more mesothelial cells, the lymphatic stomata. These are small openings of lymphatic capillaries, which are involved in immunoregulation and serve as drainage channels for active absorption of fluids and cells from the serous cavities. They are found in the greater omentum, appendices epiploicae, the peritoneal side of the diaphragm, falciform ligament, Douglas pouch and the small bowel mesentery [65]. The milky spots are distributed around the lymphatic stomata, are immunocompetent cell aggregates, and absorb peritoneal fluid through their lymphatic stomata and serve as gateways for and providers of macrophages for the abdominal cavity [66]. These structures provide a highly vascular microenvironment permitting early survival of circulating tumour cells. The production of VEGF by the mesothelium in the milky spots also promotes angiogenesis, contributing to preferential tumour growth in the milky spots [67]. However, the precise mechanisms are not well understood. The adhered free cancer cells penetrate the mesothelial monolayer either at areas of peritoneal discontinuity by invading the intercellular spaces between adjacent rounded mesothelial cells or by destroying the monolayer. The mesothelial cells become round in response to pro-inflammatory cytokines and expose their basement membrane [68]. Hepatocyte growth factor/scatter factor (HGF/SF) produced by mesothelial cells induces detachment, motility and proliferation of these cells in the process of mesothelial wound repair [25]. Binding of HGF to its tyrosine kinase receptor, encoded by the c-MET proto-oncogene, initiates an invasive growth program [69]. Destruction of the mesothelial monolayer can occur through tumour-induced apoptosis. It has been shown with an in vitro model that CRC cells adhere rapidly to the outer mesothelial monolayer. The majority of the adhered tumour cells displayed proliferative growth on the mesothelial surface without invasion. A proportion of the tumour cells invaded the mesothelium, which was characterised by apoptosis of the mesothelial cells involving membrane blebbing, cell shrinkage and nuclear fragmentation. Invasion of the peritoneal mesothelium occurs via tumour-induced mesothelial apoptosis, at least in part mediated by a Fas-dependent mechanism [70]. After penetrating the mesothelium, the tumour cells adhere to the basement membrane through integrin mediated adhesion. Integrins are calcium/magnesium dependent heterodimer molecules, consisting of α and αβ subunit, located on the cell membrane. They are involved in both homotypic cell-cell and heterotypic cell-ECM adhesion

and mediate in- and out-ward signal transduction to the actin cytoskeleton via cytoplasmic proteins [31]. Subsequent invasion of the peritoneal-blood barrier, the submesothelial tissue between the peritoneal mesothelium and the submesothelial arterial blood capillaries, occurs via degradation by proteases [68]. Tumour cells, mesothelial cells, surrounding fibroblasts, inflammatory cells and macrophages secrete matrix metalloproteinases (MMPs), which are responsible for the degradation of several ECM components [71]. Destruction of the peritoneal-blood barrier by these enzymes results from a disturbed equilibrium between the activation of pro-MMPs and their inhibition by tissue inhibitor metalloproteinases (TIMPs) [31]. Increased levels of MMP-1, MMP-2, MMP-7, MMP-9, MMP-13 and MMP-14 have been reported to play a role in the formation of PC of CRC origin. The MMPs are a family of zinc- and calcium dependent multifunctional enzymes currently comprising 23 members in humans, either membrane-anchored or secreted [72]. Many MMPs have overlapping substrate specificity and are involved in a network of mutual activation by MMPs and plasmin activation [73]. The activity of the MMPs is controlled by TIMPs [74]. There are 4 types of TIMPs. Overexpression of MMP-1 has been reported to be related to metastasis, reduced overall and/or disease free survival [75]. MMP-2 and TIMP-2 appear to play a role in the process of CRC invasion and metastasis [76]. Bidirectional signalling has been reported between mesothelial cells and tumour cells in the generation of cancer invasion. The interaction of ICAM with its ligand, CD43, has been demonstrated to play a role in both peritoneal adhesion of tumour cells and the preparation of the right environment for subsequent invasion by increasing the production of MMPs (MMP-2 and MMP-9) [77]. MMP-7 is the smallest member of the MMP family and has been proposed to fulfill a dual role in the progression of peritoneal metastases. On the one hand, MMP-7 can have a potential role in tumour invasion and metastasis by degrading basement membrane and submesothelial components. On the other hand, MMP-7 can promote the development and progression of tumour cells by inhibiting tumour cell apoptosis, decreasing cell adhesion and inducing angiogenesis [78]. MMP-13 is a useful predictor of liver metastasis in patients diagnosed with CRC [79]. Another mediator in the degradation of peritoneal-blood barrier is the urokinase plasminogen activating system, consisting of the urokinase plasminogen activator receptor (uPAR) and the urokinase plasminogen activator (uPA). uPA is a serine protease, which upon activation of the pro-enzyme (pro-uPA) catalyses the reaction in which plasminogen is converted to plasmin. Plasmin is in turn responsible for the degradation of several ECM components and the activation of pro-MMPs [80]. The catalytic activity of uPA is controlled by its inhibitors, plasminogen activator inhibitor-1 and plasminogen activator inhibitor-2, through the formation of an enzymatically inactive, trimeric receptor-protease-inhibitor complex [81]. It has been reported that uPA and uPAR are possible independent predictors of liver metastasis, overall survival, and cancer-specific survival after resection of colorectal tumours [82]. Proliferation is achieved through the production of growth factors and their receptors by tumour cells and their associated stromal cells, inducing autocrine and paracrine loops [83]. Both the epidermal growth factor receptor (EGFR) and the insulin-like growth factor-1 (IGF-1) have been reported to be involved in this process [84]. EGFR belongs to the ErbB cell surface receptor family and can be activated by several ligands including EGF and TGFα [85]. Binding of its ligand results in homo- or hetero-dimerisation of various ErbB family members, followed by internalisation of the EGFR receptor complex. Upon autophosphorylation of the EGRF tyrosine kinase domains in the cytoplasmic tails, a transduction signalling cascade is initiated, which in turn regulates tumour cell proliferation, differentiation and survival [86]. IGF-1 and its transmembrane receptor are part of a family of cellular modulators that are important in the regulation of growth and development [87]. IGF-1 has been found to be upregulated in samples of patients with peritoneal metastases [88]. For tumour growth and the formation of metastases the growth of new blood vessels from pre-existing is of the utmost importance. Tumour cells are dependent on the delivery of oxygen for their survival from pre-existing blood vessels and nutrients by the recruitment of stromal cells. Oxygen and nutrients cannot pass the peritoneal-plasma barrier if cancer cells are located more than 150μm from the submesothelial capillaries resulting in hypoxia induced apoptosis [89]. Therefore, angiogenesis is induced through the production of angiogenic factors by tumour cells [90]. In this process the keys are hypoxia inducible factor 1 (HIF-1) and VEGF. HIF-1 is a heterodimeric protein composed of HIF-1α and HIF-1β, which activates the transcription of genes involved in the induction of angiogenesis, including VEGF [91]. HIF-1β is constantly expressed and does not depend on the hypoxic status of the cells in contrast to the expression of HIF-1α which increases exponentially as oxygen levels decline in the cell [92]. High HIF-1 levels have been observed in advanced stages of CRC and were associated with increased metastatic potential [93].

The VEGF family constitutes five structurally related proteins, VEGF-A, VEGF-B, VEGF-C, VEGF-D and placental growth factor. VEGF-C and VEGF-D are important in the

process of lymphangiogenesis, while VEGF-A, VEGF-B and placental growth factor are important in neovascularization [94,95,96]. The most potent pro-angiogenic growth factor, VEGF-A binds to its receptors VEGFR-1 and VEGFR-2 and thereby increases endothelial cell survival, proliferation, migration and differentiation [97]. VEGF-A displays sensitivity to hypoxia and its expression in growing tissue is regulated by HIF [98]. It has been established that blockage of the VEGF and the EGF receptors results in decreased tumour vascularity, growth, proliferation, formation of ascites and increased apoptosis of both tumour cells and endothelial cells [99]. In addition, the investigation of tumour samples from patients undergoing cytoreduction and hyperthermic intraperitoneal chemotherapy showed that overall survival was better in patients with low VEGF expression than in patients with high VEGF expression [100].

The above mentioned metastatic steps and the molecular pathways have triggered the investigators to go on to clinical trials with systemic pharmaceutical treatments. Many of these treatments have been effective in oncological terms and have confirmed the validity of the metastatic process.

## CONCLUSION

PC is the result of a complex molecular crosstalk between cancer cells and host elements, comprising several well-defined steps, known as the peritoneal metastatic cascade. Individual or clumps of tumour cells detach from the primary tumour, gain access to the peritoneal cavity and become susceptible to the regular peritoneal transport. They attach to distant peritoneum, invade the subperitoneal space, where angiogenesis sustains proliferation and enables further metastatic growth. It is important to realize that these molecular events describe a continuous and interdependent process. A comprehensive understanding of the molecular events involved in peritoneal disease spread is of the utmost importance.

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