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TOPIC HIGHLIGHT

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# Pathophysiology and biology of peritoneal carcinomatosis

Shigeki Kusamura, Dario Baratti, Nadia Zaffaroni, Raffaella Villa, Barbara Laterza, Maria Rosaria Balestra, Marcello Deraco

Shigeki Kusamura, Dario Baratti, Barbara Laterza, Maria Rosaria Balestra, Marcello Deraco, Department of Surgery, National Cancer Institute of Milan, Via Venezian 1, 20133 Milano, Italy
Nadia Zaffaroni, Raffaella Villa, Department of Experimental Oncology, National Cancer Institute of Milan, 20133 Milano, Italy
Author contributions: Kusamura S, Baratti D, Zaffaroni N and Villa R were responsible for the conception, design and writing of the manuscript; Laterza B, Balestra MR and Deraco M were responsible for the writing and final critical revision.
Correspondence to: Marcello Deraco, MD, Department of Surgery, National Cancer Institute of Milan, Via Venezian 1, 20133 Milano, Italy. marcello.deraco@istitutotumori.mi.it
Telephone: +39-2-23902362 Fax: +39-2-23902404
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## Abstract

Peritoneal carcinomatosis represents a devastating form of cancer progression with a very poor prognosis. Its complex pathogenesis is represented by a dynamic process comprising several steps. To the best of our knowledge pathogenesis can be partly explained by 3 major molecular pathways: (1) dissemination from the primary tumor; (2) primary tumor of peritoneum; and (3) independent origins of the primary tumor and peritoneal implants. These are not mutually exclusive and combinations of different mechanisms could occur inside a single case. There are still several aspects which need explanation by future studies. A comprehensive understanding of molecular events involved in peritoneal carcinomatosis is of paramount importance and should be systematically pursued not only to identify novel strategies for the prevention of the condition, but also to obtain therapeutic advances, through the identification of surrogate markers of prognosis and development of future molecular targeted therapies.



**Key words:** Pathophysiology; Peritoneal carcinomatosis; Peritoneal mesothelioma; Pseudomyxoma peritonei; Ovarian cancer; Gastric and colorectal cancer

**Peer reviewer:** Sung-Soo Park, MD, PhD, Department of Surgery, Korea University Anam Hospital, Anam-dong 5-ga Seongbuk-gu, Seoul 136-705, South Korea

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## INTRODUCTION

Peritoneal carcinomatosis represents a devastating form of cancer progression with a very poor prognosis. The genesis of this clinical entity can be explained by several biological models and a better understanding of underlying tumor kinetics and cellular dissemination mechanisms will guide the clinical decision making process to maximize the therapeutic gains and provide resources for the development of biological targeted therapies.

In the Goldie-Coldman model, it is assumed that an initial chemosensitive population of tumor cells undergoes subsequent mutation resulting in resistance to chemotherapy[1]. Their fundamental conclusion can be illustrated by reference to the expression Px (0) = exp [-x (*N* - 1)]. At a tenable mutation rate x = $10^{-6}$, the probability of no mutants in *N* = $10^5$ cells is approximately 0.9, meaning that most low cell-loss tumor masses of $10^5$ cells are free of drug-resistant cells. However, the probability of finding no drug-resistant mutants in $10^7$ cells is only 4.5 × $10^{-5}$, meaning that it is almost certain that a $10^7$ cell mass harbors at least one drug-resistant mutant. Hence, according to this model, a growth of 2 logs can transform a drug sensitive tumor to a drug resistant tumor. The volume of $10^7$ cancer cells is approximately 0.01 mL if the whole

mass is cancer and approximately 1.0 mL if only 1% is cancer, 99% is composed of host tissues such as stromal cells, fibrosis, extracellular secretions, and blood and lymphatic vessels.

The logical development of this idea is that the best strategy is to treat a cancer when it is as small as possible, before its cells can develop resistance. This is not the case in peritoneal carcinomatosis, a clinical circumstance in which, even in early stage cases, the quantity of cells exceeds the figures mentioned above so that the probability of the presence of drug resistant clones is certain.

Thus, Goldie-Coldman is the best model supporting the rationale for cytoreductive surgery associated with hyperthermic intraperitoneal chemotherapy (HIPEC) in the treatment of peritoneal carcinomatosis. The surgical intervention enables the macroscopic resection of significant number of *de novo* resistant populations. In addition, when large tumors are reduced, the remaining tumor cells become more sensitive to chemotherapy because they become closer to the blood supply, and are more accessible to chemotherapy. Furthermore, they are stimulated to reenter the proliferative phase of the cell-cycle, becoming more susceptible to the cytotoxic effect of antiblastic therapies.

Basically there are 3 models to explain the pathogenesis of peritoneal carcinomatosis: (1) dissemination from a primary tumor (gastric and colon cancer, pseudomyxoma peritonei); (2) primary tumor of the peritoneum (peritoneal mesothelioma, serous papillary peritoneal adenocarcinoma); and (3) independent origins of the primary tumor and peritoneal implants (ovarian low malignant potential tumors, serous papillary peritoneal adenocarcinoma).

## DISSEMINATION FROM THE PRIMARY TUMOR

The tumor dissemination starts from the primary tumor and consists of a multistep process. Firstly, individual or clusters of tumor cells must detach from the primary tumor mass and gain access to the peritoneal cavity. The detachment could occur by several mechanisms and the most frequent one in gastrointestinal cancers is spontaneous exfoliation of tumor cells from cancers that have invaded the serosa. This process could be mediated by the down-regulation of intercellular adhesion molecules on the tumor cell surface, for example E-cadherin. Cadherins are transmembrane glycoproteins with an extracellular part, a membrane-spanning domain and a cytoplasmatic tail. They form a family with currently about 80 members, but information related to peritoneal carcinomatosis is now restricted to the subfamily of classical (or type I ) cadherins. In epithelial tumors the expression or the function of E-cadherin is downregulated, and this has also been confirmed for colorectal[2], gastric[3] and ovarian cancers[4] with peritoneal carcinomatosis.

The presence of viable tumor cells in the peritoneal cavity could also occur by iatrogenic or spontaneous perforation of the primary cancer[5] or from transected lymphatics and blood vessels during the course of surgical resection[6]. Once the cancer cells are seeded in the peritoneal cavity they spread to different anatomical regions of the abdomen governed by 3 basic forces: gravity, peristaltic movement of the gastrointestinal tract, and negative pressure exerted by diaphragm muscle movements.

The successive localization of intraperitoneal dissemination depends on the biology not only of free cancer cells and but also of the tissue that will harbor the metastatic implantation. The process takes place through 2 routes denominated transmesothelial and translymphatic metastasis. According to the first mechanism the free cancer cells directly attach on distant mesothelium and this process is mediated by adhesion molecules such as CD44, lymphocyte homing molecules, members of integrin superfamily, the selectins and a variety of other leukocyte associated adhesion molecules[7].

In the successive step, the production of cytokines (interleukins, EGF, HGF, VEGF-C) induces the contraction of mesothelial cells exposing the submesothelial basement membrane. Yonemura *et al*[8] investigated this phenomena using an animal model and a gastric cell line, MKN-45-P. Intraperitoneal inoculation of MKN-45-P resulted in mesothelial contraction and eventual exfoliation.

However, Jayne *et al*[9] postulated another mechanism underlying tumor- mesothelial invasion. They used a three dimensional *in vitro* model of the human peritoneum, and found that colorectal cancer cell lines adhered rapidly to the outer mesothelial monolayer. Closer inspection of points of mesothelial invasion was frequently accompanied by changes in mesothelial cell morphology suggestive of apoptosis, confirmed by DNA fragmentation assays and immunohistochemistry.

After attaching to the peritoneum and penetrating the mesothelial barrier, the tumor cells adhere to the submesothelial connective tissue through the interaction of integrins. These molecules are receptors for components of the basement membrane of cancer cells. Kawamura *et al*[10] studied the expression of various metastasis related genes (integrins subunits, motility factors, proteases, growth factors) between 2 gastric cancer cell lines: MKN-45 and MKN-45-P. The latter was characterized by its high peritoneal metastatic potential. Integrin $\alpha 2$ and $\alpha 3$ subunits were significantly elevated in MKN-45-P compared to MKN-45. These $\alpha$ integrins dimerize 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.

The invasion of subperitoneal tissue requires the degradation of the peritoneal blood barrier by motility factors and matrix proteinases. The matrix metalloproteinases (MMPs) may play a central role in stromal invasion. Yonemura *et al*[11] studied the role of MMP-7 in a mouse model of peritoneal carcinomatosis. Specific antisense oligonucleotides inhibited the expression of MMP-7 by the highly metastatic gastric cell line MKN-45P, and suppressed invasion without modifying cell proliferation. Moreover, the survival of MKN-45-P bearing mice, which had been pre-treated with antisense oligonucleotides, was significantly better than control

mice. Other potential mediators of stromal degradation are the urokinase plasminogen activating system and the protease inhibitor Bikunin (bik)[12].

Subsequently to invasion of the subperitoneal space in the vicinity of capillaries, the cancer cells trigger their proliferation through autocrine and paracrine loops by production of growth factors from cancer cells or stromal cells. Davies *et al*[13] showed that epidermal growth factor (EGF) enhanced the invasive potential of mammary carcinoma cells when injected into the peritoneal cavities of rats and that this growth promoting effect was due to the production of EGF by the peritoneal host tissue. The next step in the peritoneal dissemination process is the neoangiogenesis in the subperitoneal space which is mediated by the production of VEGF-A and VEGF-C.

Besides the transmesothelial route, peritoneal cancer dissemination could occur by another mechanism denominated the translymphatic process. According to this theory the peritoneal free cancer cells gain access to the subperitoneal lymphatic spaces through lymphatic stomata. Anatomical regions in the peritoneal cavity with a high density of lymphatic stomata are the greater omentum, appendices epiploicae of the colon, inferior surface of the diaphragm, falciform ligament, Douglas pouch and small bowel mesentery. These locations are characterized by the presence of another lymphatic structure which is involved in the translymphatic peritoneal dissemination of free cancer cells, namely the milky spots[14].

Milky spots are very small structures, in contact with the peritoneal membrane, devoid of capsule and consisting of macrophages, lymphocytes and a few plasma cells supported by blood and lymphatic vessels. The exact role of these particular organs is still not clear, but they are similar to lymphatic structures and it is clear that they play a role in peritoneal cancer dissemination[15]. Lymphatic stomata are found in the milky spots and peritoneal macrophages mobilize into the peritoneal cavity through the lymphatic orifices. The peritoneum layering the Douglas pouch, for example, is rich in subperitoneal lymphatic vessels and milky spots. The intraperitoneal fluid containing free cancer cells, once reaching the pelvic subperitoneal lymphatics, goes toward the rectum and finally flows into the lymph nodes around the iliac artery. On the other hand the peritoneum covering the liver, and the serosal surface of small bowel and spleen are devoid of lymphatic stomata as well as milky spots and thus are involved in peritoneal dissemination of cancer cells only in the late stage of peritoneal carcinomatosis.

While the mechanism of peritoneal dissemination in pseudomyxoma peritonei is characterized by the translymphatic process, the dissemination of gastric and colon cancer is characterized by both translymphatic and transmesothelial processes[16]. Pseudomyxoma peritonei is characterized by the accumulation of abundant gelatinous mucin within the peritoneal cavity and diffuse mucinous implants on the peritoneal surface and omentum. The major component of the lesions is mucinous material while neoplastic epithelial cells are extremely scanty.

In the past there was a lack of consensus about the site of origin of this clinical condition, especially in female patients. There were 3 main hypotheses: (1) metastasis from the ovary to the appendix[17]; (2) metastasis from the appendix to the ovary[18], or (3) an independent origin of the tumor[19]. In exceptionally rare cases other sites have been reported to be the primary sites, such as the colon, common bile duct, pancreas and breast[20-22]. There is a growing body of evidence, based on morphological, immunohistochemical and genetic studies, suggesting that the primary site of origin is the appendix in majority of the cases[23-27].

The most popular model explaining tumor progression advocates that an initial neoplastic process (such as a mucinous adenoma) produces mucin continuously inside the appendiceal lumen, leading to obstruction and distension of this structure. The appendix suffers rupture and the mucin material disseminates inside the peritoneal cavity guided by 3 mechanical forces: gravity, hydrostatic pressure exerted by respiratory movements of the diaphragmatic muscle and peristaltic movements of the bowel. The accumulation and deposition of the neoplastic material inside the peritoneal cavity at different locations will be conditioned by the translymphatic model of tumor dissemination, as mentioned above[14]. The biological course is indolent and progressive and leads the patient to death as a consequence of intestinal obstruction, unless adequately treated.

CDX-2 is the product of the caudal-type homeobox gene, which encodes a transcription factor that plays a role as a regulatory protein in proliferation and differentiation of intestinal epithelial cells[28]. CDX-2 expression is uniformly found in almost all cases of colorectal and duodenal adenocarcinomas[29] and appendiceal adenocarcinoma[30], whereas expression is heterogeneous in adenocarcinomas of gastric, gastro-oesophageal and pancreatobiliary origin[29,31]. Nonaka *et al*[32] reported in a series of 42 case of pseudomyxoma peritonei that all cases of peritoneal lesions, showed diffuse and strong immunoreactivity for CDX-2 in a uniform nuclear staining pattern. In a successive evaluation of this marker in the same series of patients, it was shown that immunoexpression was significantly correlated with overall survival by univariate analysis[33].

Mucins are high-molecular-weight glycoproteins, present at the interface between many epithelial and extracellular environments and synthesized by a broad range of epithelial tissues. Genes coding for the protein components of mucin are designated as MUCs. Currently 14 mucin-type glycoproteins have been assigned to the *MUC* gene family[34]. Mucins are subdivided into membrane-associated and secreted forms, the former represented by MUC-1 and the latter represented by MUC-2 and MUC-5AC. MUC-2 is specifically expressed in goblet cells of the small bowel and colon, while MUC-5AC is generally expressed in the stomach and respiratory tracts. The vast majority of mucinous epithelial neoplasms of the appendix coexpress both MUC-2 and MUC-5AC, while mucinous neoplasms of the ovary express only MUC-5AC but

not MUC-2[35]. Interestingly, cases of classic pseudomyxoma peritonei show the intestinal/appendiceal pattern (MUC- 2+ and MUC-5AC+), as do appendiceal mucinous neoplasms, whereas cases of peritoneal implants or pseudomyxoma ovarii associated with primary ovarian mucinous neoplasms show the ovarian pattern (MUC-2- and MUC-5AC+), just as ovarian mucinous neoplasms do[36]. These findings support the notion that pseudomyxoma peritonei is a disease resulting from the accumulation of extracellular secretory-type mucin, particularly related to MUC-2 overexpression by neoplastic cells, thereby rendering MUC-2 expression a potential molecular target to inhibit the progression of the disease[35,37].

## PRIMARY TUMOR OF THE PERITONEUM

Examples of primary peritoneal tumors are serous papillary adenocarcinoma of peritoneum and peritoneal mesothelioma. Inhalation of asbestos fibers has been associated with diffuse malignant mesothelioma (DMM) in humans. Despite advances in the molecular analyses of human DMM and the development of animal models, the pathogenesis of the disease remains poorly understood. There are 3 hypotheses regarding the molecular mechanisms of asbestos-induced DMM: (1) the "oxidative stress theory" is based on the fact that the phagocytic cells that engulf asbestos fibers produce large amounts of free radicals due to their inability to digest the fibers, and epidemiological studies indicating that iron-containing asbestos fibers appear more carcinogenic[38]; (2) the "chromosome tangling theory" postulates that asbestos fibers damage chromosomes when cells divide[39]; and (3) the "theory of adsorption of many specific proteins and carcinogenic molecules". According to this last model asbestos fibers *in vivo* concentrate proteins or chemicals including the components of cigarette smoke[40].

Although asbestos fibers are considered the main cause of mesothelioma, not all mesothelioma patients, especially those with the peritoneal form of the disease, have a history of exposure to this substance. This raises concerns about other possible mechanisms implicated in the genesis of mesothelioma. The calcium-binding protein calretinin constitutes a useful marker of mesotheliomas of the epithelioid and mixed types. The question as to whether the SV40 virus is involved as a possible cofactor is still highly debated. Henzi *et al*[41] have shown that increased expression of SV40 early gene products in the mesothelial cell line MeT-5A induces the expression of calretinin and that elevated calretinin levels strongly correlate with increased resistance to asbestos cytotoxicity. Calretinin alone contributes significantly to this protective effect because cells stably transfected with calretinin cDNA were shown to be more resistant to the toxic effects of crocidolite than mock-transfected control cells. The protective effect observed in clones with higher calretinin expression levels could be eliminated by phosphatidylinositol 3-kinase (PI3K) inhibitors, implying an important role for the PI3K/AKT signaling (survival) pathway in mediating the protective effect. Up-regulation of calretinin, resulting from either asbestos exposure or SV40 oncoproteins, may be a common denominator that leads to increased resistance to asbestos cytotoxicity and thereby contributes to mesothelioma carcinogenesis.

Zaffaroni *et al*[42] assessed the expression of survivin and other members of the inhibitors of apoptosis proteins (IAP) family (IAP-1, IAP-2 and X-IAP) in malignant peritoneal mesothelioma (MPM) and investigated the effects of survivin knockdown in an established MPM cell line. Expression of different IAPs was measured by immunohistochemistry. MPM cells were transfected with a small-interfering RNA (siRNA) targeting survivin mRNA and analyzed for survivin expression, growth rate, and ability to undergo spontaneous and drug (cisplatin, doxorubicin)-induced apoptosis. Survivin expression was observed in 91% of surgical MPM specimens, whereas the positivity rate for the other IAPs ranged from 69% to 100%. Transfection of MPM cells with the survivin siRNA induced a marked inhibition of survivin protein expression, a time-dependent decline in cell growth and an enhanced rate of spontaneous and drug-induced apoptosis, with a concomitant increase in the catalytic activity of caspase-9.

The same group of investigators successively conducted another study assessing the prevalence of the two known telomere maintenance mechanisms, telomerase activity (TA) and alternative lengthening of telomeres (ALT), and their prognostic relevance in diffuse malignant peritoneal mesothelioma (DMPM)[43]. One of the hallmarks of cancer cells is their limitless replicative potential. In a high percentage of human tumors, the attainment of immortality is due to the reactivation of telomerase[44], a RNA-dependent DNA polymerase that stabilizes telomeres, allows cells to avoid the senescence checkpoint, and may therefore contribute to carcinogenesis and neoplastic progression[45]. Some tumors, however, do not have telomerase activity and maintain their telomeres by one of more mechanisms referred to as alternative lengthening of telomeres (ALT) based on recombinant mediated DNA replication mechanisms[46] In particular, Villa *et al*[43] showed that telomere maintenance mechanisms were detectable in 86% of DMPM: ALT or TA alone was found in 18% or 64% of lesions, respectively, whereas 5% were ALT+/TA+. TA and ALT presented an inverse correlation ($P = 0.002$). In the overall series, TA was prognostic for 4-year relapse and cancer-related death, whereas ALT failed to significantly affect clinical outcome.

## POLYCLONAL MULTIFOCAL ORIGIN

According to this model there would be a field defect that allows a multifocal origin of the tumor. In other words the metastatic implants in the peritoneum, in the circumstance of a carcinomatosis, would have independent pathogenesis from the primary tumor. This model has been observed basically in 2 types of tumor with peritoneal involvement: ovarian tumors with low malignant potential and extraovarian papillary serous

carcinoma of the peritoneum[47,48]. On the other hand pseudomyxoma peritonei and malignant epithelial ovarian cancer have a monoclonal origin[49,50].

The clonality of a tumor can be determined by X-chromosome-linked and non X-chromosome linked analysis, such as loss of heterozygosity (LOH), gene rearrangements, and point mutations. The most consistent informative marker of the clonal composition of neoplastic disorders in women is the cellular pattern of X-chromosome inactivation. In women, normal somatic cells contain 2 X-chromosomes, one of which is inactivated during early embryogenesis. X-chromosome inactivation occurs randomly and results in somatic mosaicism in normal tissues, with an equal mix of cells inactivating the X-chromosome of either maternal or paternal origin. Throughout the life of the cell, the same maternal or paternal X chromosome will be inactivated in any subsequent cell division. Because the fidelity of the X-chromosome inactivation is retained, if the primary and peritoneal tumors arise from the same neoplastic clone, they should have identical inactive X chromosomes. Identical patterns of nonrandom X-chromosome inactivation would, therefore, suggest that the primary and peritoneal tumors are monoclonal in origin, implying that the peritoneal tumors metastasized from the primary ovarian tumor. Different patterns of nonrandom X-chromosome inactivation would suggest that the tumors are independent in origin.

There are several methods to assess X-chromosome inactivation, such as X-linked DNA polymorphism of hypoxanthine phosphoribosyl transferase (HPRT) and phosphoglycerate kinase. Another method takes advantage of the polymorphism of CAG repeats near the methylation-sensitive sites of the HhaI restriction endonuclease in exon 1 of the *androgen receptor* (*AR*) gene, located in chromosome Xq11-12[51]. The frequency of genetic polymorphism for the human *AR* gene is more than 90%, compared with 29% for that of the *HPRT* gene. The methylation status of the *Hha*I restriction endonuclease site corresponds with the inactivation status of the X chromosome and thus allows for the distinction between the active and inactive X chromosomes.

Gu *et al*[48] studied the clonality of peritoneal and ovarian tumors from advanced ovarian papillary serous tumors of low malignant potential. The polymerase chain reaction was used to amplify a CAG polymorphic site in the human AR locus on the X chromosome to determine the inactivation pattern of the X chromosome and the clonality of the tumors. They observed that 46% and 54% of tumors had respectively random and non random patterns of X chromosome inactivation in the peritoneal and ovarian tumors. Most of non random tumors had different inactivation patterns in the peritoneal and ovarian tumors. These data support the hypotheses that peritoneal and ovarian tumors of low malignant potential arise independently.

## FINAL CONSIDERATIONS

Peritoneal carcinomatosis is a complex and dynamic process comprising several steps and to the best of our knowledge its pathogenesis could be explained by 3 major molecular pathways. They are not mutually exclusive and combinations of different mechanisms could occur inside a single case. Studies on the biology of peritoneal carcinomatosis are subject to bias induced by the phenomenon of polyclonality, which is inherent to the process of neoplastic proliferation. Extending the Goldie Coldman model, large volume tumors should be expected to contain several clones with different biological properties which enable different mechanisms of neoplastic dissemination[1]. Thus, attempts to elucidate molecular mechanisms responsible for tumor progression in peritoneal carcinomatosis are extremely challenging because the identification of a single pathway does not necessary means that it is the one that determines the prognosis of the disease. The tumor specimen that is extracted for the development of cellular lines or animal models may not necessary be representative of the entire process of the patient.

Another drawback characterizing studies of the molecular biology of peritoneal carcinomatosis regards selection bias. Usually samples of the tumor are extracted from patients with a clinical condition sufficient enough to be submitted to operation. Those patients with a very aggressive disease who are addressed to supportive care do not meet the required criteria for surgical procedures which could enable the sampling of a representative and sufficient specimen for diagnostic or biological characterization. Therefore, patients with the poorest prognosis tend not to be included in studies of peritoneal carcinomatosis pathogenesis .

Anyway, a comprehensive understanding of molecular events involved in the peritoneal carcinomatosis is of paramount importance and should be systematically pursued not only to identify novel strategies for the prevention of the condition, but also to obtain therapeutic advances, through the identification of the surrogate markers of prognosis and development of future molecular targeted therapies.

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