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Peritoneal carcinomatosis: A malignant disease with an embryological origin?

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ABSTRACT

Introduction: In 1931, Simpson et al. coined the term "peritoneal carcinomatosis" to describe the regional spread of ovarian tumors as localized or extended with involvement of the peritoneal serous membrane and neighboring anatomical structures.

Research into the origin of peritoneal carcinomatosis is based on two phases in a woman's life:

Embryo development: During week 3, the bilaminar disc becomes a trilaminar disc called the mesoderm. Inside the lateral plate mesoderm, the coelomic cavity is divided into 2 layers: the parietal (somatic) mesoderm, which gives rise to the parietal peritoneum and pleural surfaces; and the visceral (splanchnic) mesoderm, which gives rise to the visceral peritoneum, visceral surface of the pleura, gonadal stroma, and the muscular layer of the hollow viscera and its mesenteries.

Tumor spread: Transcoelomic metastasis and metaplasia of pluripotent stem cells in the peritoneum was involved in the pathogenesis of ovarian cancer. This involvement takes the form of a synchronous malignant transformation at multiple foci and may cause intraperitoneal field cancerization.

Pluripotent stem cells play a role both in the development of the embryonic peritoneum and in the spread of transcoelomic tumors. Consequently, knowledge of the origin of these cells (embryonic or current) could be extremely useful.

The many markers that act during the embryonic period can affect descendants, that is, cells are already marked before specification and differentiation are activated. Thus, programmed activation could be attributed to genetic and epigenetic changes.

1. Introduction

In 1931, Simpson et al. [1] coined the term "peritoneal carcinomatosis" (PC) to describe the regional spread of ovarian tumors as localized or extended with involvement of the peritoneal serous membrane and neighboring anatomical structures. PC can be classified as gynecological (ovarian) or non-gynecological in origin (primary, gastrointestinal, and other). Between 70% and 92% of patients with epithelial ovarian cancer (EOC) present peritoneal dissemination at the time of diagnosis [2–4]; in the case of gastric cancer, this figure is 15–50% [5–7]. In PC, it is noteworthy that, while metastasis is to distant serous structures, most serous metastases presented a common embryological origin in the lateral plate mesoderm (LMP).

Histopathology, immunohistochemistry, molecular and genetic analysis show that close to 90% of ovarian carcinomas involve the epithelium. We can distinguish five main types: high-grade serous,

Abbreviations: PC, Peritoneal carcinomatosis; LPM, Lateral plate of the mesoderm; EOT, Epithelial ovarian tumor; OSE, Ovarian surface epithelium; EOC, Epithelial ovarian cancer; SCs, Stem cells; ASCs, Adult stem cells; ESCs, Embryonic stem cells; CSCs, Cancer stem cell; EMT, Epithelial-mesenchymal transition; CICs, Cortical inclusion cysts; STIC, Serous tubal intraepithelial carcinomas; TPJ, Tube–peritoneal junction.

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endometrioid, clear-cell, mucinous, and low-grade serous. The remaining 10% are non-epithelial (malignant germ cell and sex cord–stromal tumors).

Carcinogenesis in non-epithelial tumors is well established, but the exact site where the epithelial ovarian tumor (EOT) begins is unknown. EOT was traditionally thought to arise in the ovarian surface epithelium (OSE), also known as the germinal epithelium [8]. However, the three most common subtypes (serous, endometrioid, and mucinous) are morphologically and genetically identical to carcinomas of the fallopian tube, endometrium, and endocervix respectively. All three subtypes affect mullerian-derived epithelia of the female genital tract, although none of the subtypes generates ovarian tissue [9].

In 2004, based on different biological behaviors, histology findings, and molecular markers, Shih and col [10] classified ovarian cancer into two categories: type I, in which precursor lesions in the ovary are well defined, and type II, in which precursors are not clearly defined (tumors may develop from tubal and/or ovarian surface epithelium). Therefore, in 2014, the FIGO Committee on Gynecologic Oncology published a classification system for staging patients with cancer of the ovary, fallopian tube, and peritoneum [11].

EOC can spread via three main pathways: direct extension into adjacent organs, (especially the fallopian tubes, uterus, ovary, and, occasionally, the bladder and rectum), transcoelomic spread, and lymphatic spread. Distant metastasis, which is less frequent, is via hematogenous spread. Metaplasia of presumed pluripotent stem cells in the peritoneum was involved in the pathogenesis of ovarian cancer [12,13]. This involvement takes the form of a synchronous malignant transformation at multiple foci and may cause intraperitoneal field cancerization.

Recent studies criticize carcinogenesis models based on the accumulation of genetic mutations of normal somatic cells because of their simplicity [14,15] and propose an alternative theory based on genetic and epigenetic events that occur in stem cells (SCs). SCs play a role both in transcoelomic spread and in the development of the peritoneum in the embryo. Consequently, knowledge of the origin of these cells—adult or embryonic, healthy or cancerous—could be extremely useful.

2. Embryo development

2.1. Development of the ovary

The ovary is derived from multiple embryonic structures [16]: the intraembryonic coelomic epithelium covering the ovarian surface, the subcoelomic lateral mesoderm, and germ cells that migrate from the endoderm of the yolk sac. The remainder of the female genital tract, including the fallopian tubes, uterus, and upper third of the vagina, is derived from the Mullerian ducts.

2.2. Development of the lateral plate mesoderm

Generally, all structures derived from the LPM start to develop in the third week of embryonic life, resulting in small single cavities covered by the same layer. Growth and subsequent partition occur over a period of 2 weeks. The chronological order of this development is as follows [17]:

***Third week*:** The bilaminar disc becomes a trilaminar disc and then a third disc known as the mesoderm. At the end of the third week, the mesoderm is divided into three components, namely, the paraxial, intermediate, and LPM.

***Fourth week*:** A single cavity called the intraembryonic coelom is formed inside the LPM. This cavity includes all three major body cavities (pericardial, pleural, and peritoneal). The coelomic cavity is divided into two layers: the parietal or somatic mesoderm, which gives rise to the parietal peritoneum and pleural surfaces; and the visceral or splanchnic mesoderm, which gives rise to the visceral peritoneum, visceral surface of the pleura, gonadal stroma, and the muscular layer of the hollow viscera and its mesenteries.

Mesenteries are formed by a double sheet of peritoneum that starts as an extension of the visceral peritoneum that covers the organs and connects them with the body wall. During one week (28th day of embryo life), the mesenteries divide the peritoneal cavity into two parts: the right side or ventral mesenteries, which give rise to the minor omentum, falciform ligament, and visceral peritoneum of the liver, and the left side or dorsal mesenteries, which give rise to the greater omentum and spleen. The ventral mesentery disappears quickly, leaving the peritoneal cavity as a single space.

Also at the fourth week of embryo development, the diaphragm begins to form and the pleuroperitoneal canals are partitioned by the growth of the diaphragm, which separates the thorax and the abdomen at the fifth week. The diaphragm is formed centrally by a thick sheet of mesodermal tissue called the septum transversum, laterally by the ingrowth of the body wall, and posteriorly by the pleuroperitoneal folds.

The lymphatic vessels, lymph nodes, and spleen develop from the LPM during the fifth and sixth weeks.

3. Gene-expression of embryonic stem cells [ESCs]

Genetic and epigenetic changes are necessary to generate the mechanisms of cell control required to regulate the pluripotent status of ESC and the tumorigenic transformation from CSs to cancer stem cells [CSCs], as well as to activate the epithelial–mesenchymal transition [EMT] program.

- **Epigenetic change** is considered a heritable alteration in the expression of a gene that does not involve a change in DNA structure. Epigenetic changes occur via DNA or histone methylation. While the first event is a unidirectional process that prevents binding of transcription factors and prompts a closed chromatin structure, the second is crucial for activation or suppression of gene expression. The early embryo is subject to alternating decreased and increased DNA methylation stages in a major event known as reprogramming [18], which enables cell differentiation and full embryo development. Through DNA methylation, embryonic cells acquire stable and heritable DNA modifications. Hypermethylation is involved in gene silencing [19] (not always in the appropriate direction, e.g. silencing of tumor suppressor genes); whereas hypomethylation is associated with carcinogenesis [20]. Cancer is characterized by a methylation imbalance, which can lead to increased chromosomal instability and mutations. Recent studies on the human embryo suggest a close relationship between embryogenesis and tumorigenesis [21]. In experimental studies, cancer has been generated in offspring by introducing retroviruses in the ESCs [22].
- **Pluripotency in ESCs** results from a gene-expression program mediated by specific transcription factors, chromatin-modifying enzymes, regulatory RNA molecules, and signal-transduction pathways. The transcription factors involved in the early development and identity of ESCs are Oct4, Nanog, and Sox2. The transcribed genes implicated in maintaining stemness are Hesx1, Zic3, and Stat3. The silent genes responsible for cell differentiation in the three embryo layers are Pax6, Meis1, and HoxB1 in the ectoderm, Dlx5 and Hand1 in the mesoderm, and Atbf1 in the endoderm [23]. Furthermore, polycomb-group proteins are epigenetic regulators that facilitate pluripotency