**PANCREATIC CANCER (CP).
New concepts for CP etiopathogenesis. The beneficial role of gemotherapy.**                                                      Dr. Didi SURCEL

Pancreatic Cancer (CP), one of the most aggressive cancers, is characterized by an intense stromal desmoplastic reaction that surrounds cancer cells.
With all advances in the last decade, PC is frequently diagnosed late and is associated with a high mortality rate. The process of tumor micromedium (TME) evolution, including the dynamic biological behavior of various types of cancerous and stromal cells, along with the wide and diverse range of immune cells, is the constantly involved factor in PC development. Although CP etiology and pathogenesis remain unclear, genetic load and environmental factors are constantly involved in CP initiation and progression, with the statement that intracellular pathway involvement, such as STAT3 and NFkB, holds an important role. Genomic instability is a prerequisite for cancer development. It occurs when genomic maintenance systems fail to protect the integrity of the genome, either as a consequence of defects inherited or induced by exposure to environmental agents (chemicals, biological agents and radiation). Thus, genome instability can be defined as exposure to low doses of other chemical substances present in our modern society that could contribute to carcinogenesis by indirectly affecting genome stability. The basic players in CP induction and development are:
 1) STROMAL CELLS, and in particular cancer-associated fibroblasts (CAFs), which are the major effector cells of the desmoplastic reaction and the pancreatic stem cells, are the most important source of CAF.

CAF, initially known as carcinoma-associated fibroblasts, plays a significant role in the growth and progression of tumors. These cells exhibit a miofibroblast-like phenotype, characterized by a spherical shape and expression of α-actin α-actin molecules of smooth muscle (α-SMA). Functionally, this class of fibroblasts (CAF) is characterized by the production of a wide variety of molecules, such as extracellular matrix (ECM), growth factors, cytokines and chemokines.integrins, adhesion molecules. Recent publications draw attention to the fact that the desmoplastic stroma PC cells against chemotherapy and radiotherapy and that it could promote the proliferation and migration of PC cells.
2) INFLAMATORY CELLS, of which a major role is associated with cancer-associated macrophages (CAM), the presence of mast cells, the neutrophil N2 subtype associated in early stages of cancer development, dendritic cells and NK cells, both cell types with much reduced functional capability, along with myeloid-derived overload cells (MDSC)
3.) IMMUNE CELLS are major involved in CP development. Inflammation may favor the formation of premalignant lesions and accelerate the development of pancreatic cancer. CP is characterized by an immunosuppressive environment that appears to be responsible for tumor promotion, progression and metastasis. Immunosuppression is ensured by the involvement of both innate and adaptive immune cells
Pancreatic adenocarcinoma is characterized by marked immune dysfunctions driven by immunosuppressant cell types, immune cells that promote tumors and defective or even absent inflammatory cells. Recent studies have shown that immune cells interact with cancer stem cells and tumor stromal cells, and these interactions have a major impact on the development and progression of pancreatic ductal adenocarcinoma (PDAC).

In the PDAC there was a decrease in the subpopulation of CD4 + T lymphocytes
and CD8 + T lymphocytes and an increase in LT reg. cells.
The current literature describes the role of immune response in the progressive development of pancreatic cancer, emphasizing the mechanisms that lead to the recruitment and activation of immune cells at the site of the tumor and to their training in the direction of tumor protection. Recent clinical and preclinical data detail the involvement of immune responses in pancreatic cancer, including the role of specific cytokines with their implications for the pathogenic mechanism of the disease.Numerous papers highlight the interaction of immune cells and tumor micromedies, emphasizing their role in tumor growth and metastasis. A study by researchers at the University of North Carolina Lineberger Comprehensive Cancer Center provides new details on the development of a particular immune cell that can play a major role in cr diseases. inflammatory conditions, such as cancer or autoimmune diseases.
The researchers reported in the journal Nature new details about what triggers the development of a Th17 subtype, a T-helper CD4 cell. This cell subtype sends signals to attract additional help to the site of the tumor or infection. The first step is the interleukin-6 signal, which allows the expression of a gene that is essential for the development of the Th17 subtype. A Ski-Smad4 molecular complex has also been discovered, and as TGF-beta signaling, Ski-Smad4 is launched. The researchers said that while interleukin-6 is an accelerator. lead the expression of Th17, the molecular complex Ski-Smad4 is like a brake to be released.
Immunological editing is one of the key issues for which tumors avoid immunological surveillance and thus tumors remain latent for years by "balance" and "senescence" before renewal. In addition, tumors exploit many immunological processes, such as regression T reg. , or their secretions of cytokines, kemochines, antigen presentation, modification of suppressive mediator production, immune tolerance and other abnormalities. In addition, metastases also play a critical role in tumor growth.
Knowing that not all cancer cells in tumors have the same potential for tumor growth / cancer cell concept and tumor cell heterogeneity / is about to revolutionize how we understand the interaction between stromal, immune and cancer cells and new treatment options cancer patients. The focus of this review is on the role of cell adhesion molecules (CAMo) in the interaction between stem cell cancer (CSC) and extracellular matrix (ECM) as well as changes in the expression profile of the adhesion molecules, because cancer cells leave the mayor and pass in the next stage of metastasis.
The development and progress of cancer is facilitated by numerous factors besides the above, environmental factors, diet, genetic loading and epigenetic alteration along with genetic loading. Knowledge of cancer biology, genetic and epigenetic aspects has led to reclassification of cancers, first of all knowing that not all cancer cells within tumors have potential equal to tumor growth, the concept of cancer stem cells (CSF) and cell heterogeneity tumor.
Other important and constant factors involved in CP development are:
4) **ENDOTELIAL CELLS
5) EPITELIAL-MEZENCHIMAL TRANSIT
6) MICROBIOTA**

Although PC etiology and pathogenesis remain unclear, both genetic susceptibility and environmental factors are involved in PC initiation and progression. Recent studies with experimental models in animals and clinical patients have indicated that intestinal microbiota is one of the critical environmental factors that influence nutrient metabolism, immune responses and host health in various diseases of the digestive system, including the pancreas, which does not have a own microbiota. Recent data highlight a permanent crosstalk between the intestinal microflora and the immune response of the host, with the implication of this interaction in PC pathogenesis.

7) **ANGIOGENESIS** is induced and sustained mainly by hypoxia.
Tumor and tumor stromal cells produce a series of pro-inflammatory and pro-angiogenic cytokines (tumor necrosis factor, VEGF-A, interleukin-8.

**8) THE ROLE OF CELLULAR ADHESION MOLECULES (CAMo)** in the interaction of cancer cells (stem cells) and extracellular matrix (ECM) as well as changes in the adhesion molecule expression profile because cancer cells leave the primary tumor and travel to form metastases.
**9) PROTINS** play an important role in the evacuation of proangiogenic factors in ECM and the stimulation of angiogenic inhibitors. Angiogenesis is induced by hypoxic conditions that stabilize inducible hypoxia factors (HIF-1a and HIF-2a). The activation of certain oncogenes, kinases (e.g., phosphoinositide 3-kinase) or tumor suppressor genes (i.e., VHL, PTEN) also induce HIF-1α accumulation. The four CAM families, including integrins, cadherins, selectins and IgSF members, are involved in tumor angiogenesis. Endothelial selecines, a membrane glycoprotein, play a key role in the adhesion of leukocytes to endothelial cells activated by cytokines.
 The researchers hope that the new findings will be real help in looking for new and effective treatments for CP patients.

Until then, alternative treatments such as gemotherapy, which means the use of plant stem cells, can be of real use given the anti-inflammatory, immunomodulatory, antioxidant effect, repair of the structure and function of the damaged tissue and especially their antifibrotic, antisclerotic and vascular bed restoration and functional and structural affected capacity.