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Chemoprevention and Treatment of Pancreatic Cancer

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Editorial

Pancreatic cancer (PC) is the fourth leading cause of cancer death, with a median survival of 6 months and a dismal 5-year survival rate of 3-5%, and this figure has remained relatively unchanged over the past 25 years. Even for those patients diagnosed with local disease, the 5-year survival rate is only 15%. Thus, PC is one of the most difficult diseases to treat due to late initial diagnosis and to resistance to the usual treatments [1]. The presence of occult or clinical metastases at the time of diagnosis, together with the lack of effective chemotherapies, contributes to the high mortality in patients with PC. Its lethal nature stems from its propensity to disseminate rapidly to the lymphatic system and distant organs. Moreover, PC is one of the most intrinsically drug-resistant tumors and the cancer cell resistance to chemotherapeutic agents is a major cause of its treatment failure. Gemcitabine (a nucleoside-based compound) is the standard chemotherapeutic drug for patients with an advanced illness state after a phase III trial in 1997. This trial demonstrated a modest survival advantage of this agent over 5-fluorouracil (median survival 5.65 vs. 4.41 months, respectively), but surprisingly this treatment improved alleviation of disease-related effects. Known risk factors for the disease include cigarette smoking, chronic and hereditary pancreatitis, late onset diabetes mellitus, and familial cancer syndromes. However, it has been estimated that more than two-thirds of human cancers, and among them PC, could be prevented by modification of lifestyle, including dietary modification [2].

The dietary factors that are associated with increased risk of PC are meat, red meat in particular and large intakes of high-energy food. Protection is mainly provided by fruit, vegetables, and vitamins. In recent years, more dietary compounds have been recognized as cancer chemopreventive agents because of their anticarcinogenic activity; therefore, early invasion and metastasis of PC could be preventable by these dietary compounds. For instance, the ingest of curcumin, found in a plant widely cultivated in tropical regions of Asia and Central America, and known by its pronounced anti-inflammatory, antioxidative, immunomodulating, antiatherogenic, and anticarcinogenic activities, modulates, among other proteins, the activity of NF-κB through inhibition of IKK activity in PC cells, and it further alters the expression of miRNAs in PC cells. Moreover, the dietary addition of genistein, a soy isoflavone found in soybeans and in most soy-protein products, inhibited NF-κB DNA-binding activity, the Akt activity, and significantly down-regulated Notch signaling, leading to the inhibition of NF-κB and induction of apoptosis in PC cells [3]. The intake of indole-3-carbinol, green tea catechins, lycopenes, and resveratrol (all of them present in several plants) has also been shown to be valuable in the prevention of PC. It is interesting to note that the experimental results with soy isoflavones, indole-3-carbinol, curcumin, and resveratrol appear to target similar signaling pathways, all of which are known to be involved in the development and progression of PC and, therefore, they are important targets for its prevention and/or treatment. However, it is important to keep in mind that primary prevention of PC is not feasible due to lack of identifiable risk factors. Notwithstanding this fact, existing knowledge provides sufficient information as to the novel application of several dietary or nutritional agents for the prevention of illness progression. In addition, these agents could be also useful for the treatment of PC, either as single agents or in combination, especially with existing therapeutic drugs. Due to the absence of powerful treatments for PC, there is a dire need for the design of new and targeted therapeutic strategies that can overcome the drug resistance and improve the clinical outcome for patients diagnosed with the illness. To this end, the knowledge of the molecular aspects of PC is very important, and it is likely to be helpful in the design of newer drugs and the molecular selection of existing agents for targeted therapy. In the papers comprising this series devoted to PC, several leading groups from different world-wide laboratories have summarized what we know regarding the molecular aspects of the illness, and how some of those molecular pathways could be exploited for the prevention and/or treatment of PC. The several reviews tackle different aspects of PC, from the new antibody (AB) therapies to the more ground-layer aspects of structural biology, or encompassing the importance of metastasis in PC, to the influence of ubiquitylation in the development of the illness. Intensive investigation of molecular pathogenesis will aid in identifying useful molecules for diagnosis, treatment, and prognosis of PC. Mutations, which appear more frequently in PC, lead to structural changes in the proteins involved, hampering the cross-talk with other proteins and, then, resulting into inactivation. This inactivation is especially important in several tumor-suppressor genes (as in p16, SMAD4, or p53 pathways) [4]. Furthermore, the knowledge of the atomic details of the structure provides us with new arms to design more efficient drugs. For instance, in EGFR signaling, the phosphorylation of EGFR activates molecules in different cell signaling pathways, including the PI3K, Srcs, MAPK, and STAT; these pathways are involved in cell cycle progression, cell division, survival, motility, invasion, and metastasis. Knowing how and where (i.e., which residues are involved) phosphorylation at the molecular level occurs has led to the design of erlotinib, a small molecule inhibitor of the EGFR tyrosine kinase. Experimental studies have shown that erlotinib inhibits EGFR tyrosine kinase activity and cell growth in PC cell lines and in an animal model. In a phase III trial for patients with advanced PC, erlotinib together with gemcitabine has shown a statistically significant survival benefit compared with gemcitabine alone. In another study combining erlotinib with gemcitabine and irradiation for locally advanced unresectable PC, most of the examined patients showed disease stabilization.

Finally, when combined with capecitabine, erlotinib has shown considerable antitumor activity and better tumor control in a phase II trial for advanced PC. The inhibition of signal pathways can be

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carried out not only by small molecules, able to bind to selected regions of the target protein, but also by using large molecules as ABs. This is the topic described by Chames and coworkers [5]. The VEGF (vascular endothelial growth factor) protein, which is involved in angiogenesis during tumor growth and dissemination, is one of the first examples where an AB (called bevacizumab) has been designed to hamper binding to its receptor (VEGFR). EGFR is the other example described by Chames and colleagues. Cetuximab, a monoclonal AB that targets EGFR, binds to EGFR competitively with high affinity, preventing activation of EGFR by its ligands. By binding to EGFR, cetuximab inhibits cell proliferation, enhances apoptosis, and reduces angiogenesis and invasion. Cetuximab is currently under investigation in PC; the combination of cetuximab and gemcitabine showed promising activity against an advanced illness and improved survival in animal study, but it was ineffective in a phase III trial in patients with locally advanced and metastatic PC. No objective responses were seen in phase II trials of cetuximab in combination with gemcitabine and intensity-modulated radiotherapy. Trastuzumab, an anti-HER-2/neu AB, showed cell growth inhibitory activity against human PC cell lines and antitumor activity in an orthotopic mouse model. Mesothelin and carcinoembryonic antigens are two other proteins where initial steps towards the design of ABs have been given. Preclinical studies and the design of new ABs against the epithelial cell adhesion, nonspecific cross-reacting antigen, mucin-1, or death receptor 5 have also shown promising results; they induce, among other effects, apoptosis via caspase activation. It has been indicated above that by hampering phosphorylation, we are able to alter several signaling pathways where EFGR intervenes, but this is not the sole protein modification that can have dramatic results in PC development. Soubeyran and colleagues describe the importance of ubiquitylation.

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