Pancreatic Cancer Chemoprevention: Challenges and Opportunities

Pancreatic cancer (PC) is a highly aggressive cancer usually diagnosed at an advanced stage, and has the worst prognosis of any cancer malignancy, with a 5-year survival rate of <8%. Lack of early detection and effective interventions are major factors contributing to the poor prognosis and dismal survival rates of pancreatic cancer patients. Moreover, recent incidence and mortality rates suggest an increasing trend of pancreatic cancer patients.

Recent developments demonstrate that pre-invasive precursors, such as PanINs, IPMNs, and cystadenomas, progress slowly over many years to develop into invasive pancreatic cancers. Thus, there is a time frame of several years for effective chemoprevention and intervention strategies. Despite many advances in the molecular genetics of human pancreatic cancers, targeted therapies have not yet translated to improved overall survival. Hence, developing chemoprevention strategies that delay/inhibit/prevent the progression of each subtype of pre-invasive lesions to pancreatic cancer is of utmost importance. Several genetically engineered mouse models (GEMs) of pancreatic cancer that recapitulate human disease progression have recently been developed. The KrasG12D and KrasG12V dependent GEM models which mimic the therapeutic response of human pancreatic cancer offer novel treatment development opportunities. The biggest challenges are to elucidate the regulatory mechanisms controlling the progression of pancreatic precursor lesions to pancreatic cancer, and to develop strategies that provide effective chemoprevention. Equally challenging is identifying high-risk cohorts with specific pancreatic precursor lesions using early detection approaches.

In this special issue, different aspects of this problem are presented focusing on current challenges and opportunities aimed to address chemoprevention aspects for pancreatic cancer. Possible pancreatic cancer chemoprevention targets, mouse models and early detection, immuno-prevention of pancreatic cancer, drug candidates for pancreatic cancer chemoprevention, regulatory mechanisms controlling pancreatic cancer progression, combination chemoprevention strategies and different approaches are also considered and discussed.

The first review by Mohammed et al addresses the current challenges and potential opportunities for chemoprevention of pancreatic cancer. In this review, they focused on the current situation of PC, the potential challenges, the progress in existing strategies and available opportunities, as well as suggested key areas for research within the increasingly important area of pancreatic cancer chemoprevention. They suggested that novel technologies such as next generation sequencing should be employed to identify high-risk individuals with early genetic changes in the initial lesions or even explored in blood samples to detect the presence of circulating tumor derived or related mRNA, miRNA, DNA, tumor educated platelet-mRNA as biomarkers of early detection. GEM serve as excellent models to study the early stages of PC and for early detection by molecular imaging technologies. GEM models should be extensively utilized for developing existing chemoprevention agents or screening and optimizing new agents and identifying ideal chemoprevention targets. High-risk individuals presenting IPMN/PanINs and those with hereditary PC history should be considered for chemopreventive clinical trials. Combination chemoprevention, multi-targeted agents and multi-agent low dose chemoprevention strategies might be considered to reduce toxicity and enhance efficacy.

The contribution by Dhar et al. takes into consideration the mechanisms and drug targets for pancreatic cancer chemoprevention. They discussed the available drugs and their limitations, and move on to discuss the wide realm of chemopreventive efficacy that natural agents offer. While the intake of fruits and vegetables in routine diets has been linked to reduced risk of developing pancreatic cancer, a wide variety of natural agents is being evaluated as adjuvant therapies in combination with frontline chemotherapeutics in pancreatic cancer clinical trials. Completed and ongoing human studies with these natural agents have shown surprisingly successful rates for regulating pancreatic carcinogenesis. Furthermore, the underlying mechanisms of action and available information from extensive literature analysis to highlighting the novelty of these agents for their antitumor effects against pancreatic cancer, are elucidated.
In the review by Hildegard, the regulatory role of G protein-coupled receptors in pancreatic cancer development and progression are described. Smoking, psychological stress, diabetes, pancreatitis and alcohol abuse are known risk factors for pancreatic cancer that cause hyperactive cyclic adenosine monophosphate (cAMP) signaling via a beta-adrenergic and prostaglandin (PG) E2 receptors and/or by suppressing signaling via inhibitory Gαi-coupled GABAB-receptors. The activation of Gαi-coupled GABAB-receptor signaling by treatment with GABA, inhibition of β-adrenergic signaling by a beta-blocker and/or suppression of Gαs-coupled PGE2 receptor signaling by a cyclooxygenase (COX) inhibitor prevented the development and progression of PC in hamsters induced by carcinogenic nitrosamines and in transgenic mice. The re-purposing of cardiovascular therapeutics (beta-blockers, COX-2 inhibitors, Ca2+-channel blockers) that inhibit β-adrenergic and PGE2 signaling for PC intervention is problematic due to undesirable side effects under chronic treatment protocols. To avoid such side effects while effectively reducing excessive cAMP signaling, nutritional GABA supplementation or positive allosteric modulators (PAMs) of Gαi-coupled receptors (GABAB-Rs) currently in clinical trials for the treatment of addiction should be explored for pancreatic cancer intervention.

Rao et al. review discusses the novel approaches of immunoprevention for PC. Vaccine-based treatments for several cancers are currently under intense investigation. Current vaccine testing for PC is usually performed in advanced stages of cancer, during which the patient's impaired immune responses improved to suppress the growing tumor. However, so far such strategies have had limited success and have not become mainstream therapies. Thus, early diagnosis is imperative for immunoprevention using vaccines. Developing vaccines towards non-self-antigens has been successful, whereas vaccines against self-antigens, without any adverse effects on normal cells, have been challenging. The development of new technologies to identify mutated antigens, post-translational alterations in proteins, and tumor-specific antigens is currently underway, with a view toward vaccine development. Combining vaccines with immune stimulators or non-toxic anticancer agents are promising for cancer prevention. Successful vaccination strategies for PC at different stages of tumor development and future challenges for immunoprevention are discussed in this review.

Along this line, the paper by Subramaniam and co-authors reviewed approaches to target cancer stem cells for chemoprevention of pancreatic cancer. Emerging evidence supports the presence of a unique population of cells called cancer stem cells (CSCs) as potential cancer inducing cells and efforts are underway to develop therapeutic strategies targeting these cells. Studies have been shown that CSCs are highly resistant to standard therapy and responsible for drug resistance, cancer recurrence and metastasis. To overcome this problem, novel preventive agents that target these CSCs are needed. Natural compounds or phytochemicals have the ability to target these CSCs and their signaling pathways. Therefore, they summarized current understanding of pancreatic CSCs and their signaling pathways, and the phytochemicals that target these cells including curcumin, resveratrol, tea polyphenol EGCG (epigallocatechin-3-gallate), crocetin acid, sulforaphane, genistein, indole-3-carbinol, vitamin E δ-tocotrienol, Plumbagin, quercetin, triptolide, Licofelene and Quinomycin. These natural/synthetic compounds or phytochemicals, which inhibit cancer stem cells, may prove to be promising agents for the prevention and treatment of pancreatic cancers.

Together with the data summarized by Yu et al., the paper provides a systematic literature review and meta-analysis on the effect of metformin and statin use on survival in PC patients. Current epidemiological studies report conflicting results for the effect of statin or metformin on overall PC survival. They systematically searched for studies about the association between statin or metformin use and overall pancreatic cancer survival in electronic databases. A meta-analysis based on hazard ratios (HRs) and 95% confidence intervals (CIs) was performed using random effect models. Heterogeneity between the studies was examined using I2 statistics, and sensitivity analyses were conducted to assess the robustness of the findings. Of 116 statin-related articles identified, 6 retrospective cohort studies representing 12,057 patients were included. There was significant heterogeneity between the studies. Statin use was associated with improved survival among pancreatic cancer patients. Of 311 metformin-related articles, 8 retrospective cohort studies and 2 randomized clinical trials, representing 3,042 patients were identified. Metformin use was associated with better overall survival among pancreatic cancer patients (meta-HR = 0.79; 95% CI: 0.70, 0.92, P < 0.001), and significant heterogeneity was observed between the studies. These findings suggest that the improved survival time of pancreatic cancer patients is associated with statin or metformin use. Due to the multiple sources of heterogeneity of the original studies, these findings should be considered cautiously, and confirmed with larger prospective individual-level studies.
The last review by Torres and co-authors focused on the complexity of omega-3 fatty acids modulation of signaling pathways related to PC. Recently, the role of nutrition in health and disease has attracted much attention. Several dietary ingredients are involved in metabolic, physiological, and cellular signaling affecting tumor growth and progression. Although lipids, and more specifically polyunsaturated fatty acids, have been traditionally studied due to their health effects in cardiovascular disease, it is now clear that they can affect an extensive array of cellular processes that influence a wide range of diseases such as type II diabetes, inflammatory disorders and cancer. These biological activities may be grouped as regulation of membrane structure and function, intracellular signaling pathways, transcription factor activity, gene expression, and production of bioactive lipid mediators. In this review, specifically, the current state of knowledge about the potential mechanism(s) of action and signaling pathways modulated by polyunsaturated fatty acids in pancreatic cancer are discussed.

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