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Editorial

Cancer risks and perspectives: Molecular mechanisms

Strategies for the intervention and prevention of cancers, diabetes, cardiovascular diseases, HIV/AIDS and other diseases of overt inflammation including neurodegenerative diseases (Alzheimer's and Parkinson's disease) require an understanding of the basic molecular mechanism(s) by prophylactic agents (dietary antioxidant factors from food plants and medicinal plants in this context) that may potentially prevent or reverse the promotion or progression of the diseases [1,2]. Cancer is a group of diseases characterized by uncontrolled cell proliferation, evasion of cell death and the ability to invade and disrupt vital tissue function. Cancer cells can spread to other parts of the body through the blood and lymph systems. The main types cancer include: Carcinoma (which characterizes cancers that begin in the skin or in the tissues that line or cover internal organs with subtypes of carcinoma, including adenocarcinoma, basal cell carcinoma, squamous cell carcinoma, and transitional cell carcinoma), Sarcoma (which characterizes cancers that begin in bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue), Leukemia (which characterizes cancers that start in blood-forming tissue such as the bone marrow and cause large numbers of abnormal blood cells to be produced which then enters the blood), Lymphoma and Myeloma (which characterizes cancers that begin in the cells of the immune system) and Central nervous system cancers (which characterizes the cancers that begin in the tissues of the brain and spinal cord). Cancer arises from a loss of normal growth control. In normal tissues, the rates of new cell growth and old cell death are kept in balance. In cancer, this balance is disrupted resulting from uncontrolled cell growth or loss of a cell's ability to undergo apoptosis or cell suicide whereby old or damaged cells normally self-destruct. The classical model of carcinogenesis describes successive clonal expansion driven by the accumulation of mutations that eliminate restraints on proliferation and cell survival. Older cancer patients have variable physiologic ages necessitating the need to individualize their treatment for better outcome [3,4].

Given the increasing number of cancer survivors, there is a trend to shift patient care from a model that was focused on the immediate need to treat the tumor to a more holistic approach that aims to ensure both quantity and quality of life. The key tenets of quality of life are often associated with communication, trust, caring behavior, comfort, and social and spiritual support. Getting inadequate health information and lack of psychosocial care coupled with lack of and/or delay in coordinated care are among the barriers to quality care that a cancer patient may receive. From the healthcare provider's perspective, workload or administrative burden, lack of coordinated care, bureaucracy of managed care and lack of processes to support treatment guidelines tend to impact the quality of care received by the patient. These are often impacted by strategies being implemented by managed care to address cancer quality, which include decision support tools, pathways, guidelines, and cost reduction strategies (reviewed in [5]). In treating cancer, toxicity from systemic therapy with chemotherapeutic drugs and severe complications from radiation therapy are two most critical limiting factors associated with patient safety. This has led to seeking alternate chemopreventive approaches through dietary means and/or use of pharmacological and natural agents whose multiple intervention strategies, efficacy and acceptable toxicity are potentially anticipated to arrest or reverse the cellular and molecular processes of carcinogenesis. In this vein, progress in understanding the molecular changes that underlie cancer development offer the prospect of specifically targeting malfunctioning molecules and pathways to achieve more effective and rational cancer therapy.

While the first-line therapy for advanced non-small cell lung cancer is platinum-based chemotherapy, patients with specific mutations may effectively be treated with targeted agents initially. In the treatment of patients suffering from advanced cancers with contemporary systemic therapies, the challenge is to attain therapeutic efficacy, while minimizing side effects. The side effects may range from nausea to tissue damage. In cancer survivors, the iatrogenic outcomes may include consequences of genomic mutations in patients themselves or their children. Thus the main challenge for the oncologists is not to cross the thin line between eradicating cancer cells *in vivo*, in the patients' bodies, but not harm these patients' healthy cells. This is a particularly tough challenge in advanced cancers, which metastasize to multiple and distant locations of the patients' bodies. In this realm, there is a great promise in genetic engineering of stem cells (compatible with the patient's immune system) guided to the specific tumour to deliver the therapeutic trans-genes into cancer cells to induce their death. The advanced stages are often beyond the therapeutic arsenal of local surgery, but require systemic therapies associated with severe side effects [3–7].

The seminal reviews, commentary and research papers contained in this Special Issue highlight developments to not only understand cancer but to treat the disease with a view to the minimization of side effects of such therapies. Commentaries deriving from the various articles therein are here presented as an introduction to the reader.

The "regression" of cancer cells involves changes within metabolic machinery and survival strategies, which enables the cancer cells to behave as selfish "neo-endo-parasites" that exploit

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the tumor stromal cells in order to extract nutrients from the surrounding microenvironment. Thus, anti-parasitic compounds might serve as promising anticancer drugs. Nitazoxanide (NTZ), a thiazolide compound, has shown antimicrobial properties against anaerobic bacteria, as well as against helminthes and protozoa. NTZ has also been successfully used to promote Hepatitis C virus elimination by improving interferon signaling and promoting autophagy. NTZ seems to be able to interfere with crucial metabolic and pro-death signaling such as drug detoxification, unfolded protein response, autophagy, anti-cytokine activities and c-Myc inhibition. Thus the ability of NTZ to interfere with integrated survival mechanisms of cancer cells ascribes it a unique chemotherapeutic strategy against cancer.

Prostate cancer (PCA) is a leading cause of cancer-related deaths among men in the United States. Patients with localized PCA have a very high 5-year survival rate; however, in patients with clinically detectable metastatic disease, median survival is mostly reduced to 12–15 months. Thus preventing or inhibiting metastasis through nontoxic agents could be a rationalized approach for lowering high mortality among PCA patients. The natural flavonoid silibinin possesses strong anti-metastatic efficacy against PCA but its mechanism/s of its action still remain uncharacterized. One of the major events during metastasis is the replacement of cell–cell interaction with integrins-based cell–matrix interaction that controls motility, invasiveness and survival of cancer cells. Emerging data from studies on advanced human PCA PC3 cells' interaction with extracellular matrix component fibronectin indicate that Silibinin treatment significantly decreased the fibronectin-induced motile morphology via targeting actin cytoskeleton organization in PC3 cells. Integrins recognize and bind specific ligands (such as fibronectin, vitornectin, collagen and laminin) resulting in clustering of integrins and recruitment and activation of signaling/adaptor molecules such as focal adhesion kinase (FAK), Src, integrin-linked kinase (ILK), PI3K/Akt, Ras/MAPK and Rho family of GTPases (Rac, Rho and Cdc42, etc.). These signaling cascades regulate a variety of cellular processes including cell adhesion, shape, EMT, migration, proliferation and apoptosis. Silibinin decreases the fibronectin-induced cell proliferation and motility but significantly increased cell death in PC3 cells. Thus silibinin targets PCA cells' interaction with fibronectin and inhibits their motility, invasiveness and survival, hence supporting silibinin use in PCA intervention including its metastatic progression.

Oncologists and diabetologists quote scientific data from epidemiological and in *vitro* studies to show that high levels of insulin and glucose, in combination with oxidative stress and chronic inflammation, can heighten the risk of developing cancer amongst patients with diabetes. Although the cancers that have been consistently associated with type 2 diabetes include pancreatic, colorectal, breast and liver cancers, the preponderance of the disease risk factors such as obesity, inflammation, hyperglycemia, hyperinsulinaemia (as a result of insulin resistance and oxidative beta-cell damage) and the indirect influence of anti-diabetic medications are increasingly being defined. Experimental studies exploring the responsiveness of tumor growth to exogenous glucose are generally in agreement that hyperglycemic conditions indeed favor cell growth, anti-apoptosis, increased cell motility and boost invasiveness. The promotion of early-stage breast and prostate tumor growth under the influence of hyperinsulinemia is frequently related to the shared involvement of IGF-1 and IGFBP-3 receptors in phosphatidyl inositol 3-kinase (PI3K)/AKT and mitogen-activated protein kinase (MAPK) signaling pathways. Insulin resistance may also trigger cancer development via other mechanisms such as: over expression of estrogen, interleukin-6, leptin, TNF-alpha and plasminogen activator inhibitor-1. This theoretically suggests that normalization of glucose levels through insulin therapy could possibly constrain cancer progression. Fermented papaya preparation (FPP) has defined antioxidant and immune-modulating potentials. The ability of FPP influence signaling cascades associated with cell growth and survival presents a rational for chemopreventive adjunct that can be used in combination with traditional redox based therapies that target oxidative stress in the cancer micro environment. It is possible that cancer cells may develop some form of resistance during persistent reactive oxygen species (ROS) attack, rendering them more aggressive and resistant to chemical eradication. For example: continuous exposure of bladder cancer cells to arsenic trioxide (As_2O_3) resulted in cancerous cells surmounting its genotoxic effects. It was found that the influence of As_2O_3 enhanced the activation of cell's intrinsic antioxidant system and promoted the expression of cell survival proteins (e.g. reduced glutathione) – a chain reaction involving transcription factors [8]. It is therefore interesting that the concept of ROS dependent mitogenic and anti-apoptosis signaling pathways represents a specific vulnerability that can be selectively targeted by antioxidants, representing a novel class of potential agents that could effectively eliminate cancer cells. Novel bioactive components including benzyl glucosinolate identified in aqueous extract of papaya exhibit anti-growth activity on several tumor cell lines. The demonstrated efficacy of FPP to control blood glucose, excessive inflammation and modulate free radical-induced oxidative damage which are triggers of liver, bladder, breast and prostate cancers in type 2 diabetes patients, may favorably mitigate the side effects of ensuing diabetes and cancer therapy. The following comments on proanthocyanidins, address the context of other neutraceuticals in this vein.

The therapeutic benefits of grape seed proanthocyanidins (GSP) against oxidative stress and degenerative diseases including cardiovascular dysfunctions, acute and chronic stress, gastrointestinal distress, neurological disorders, pancreatitis, various stages of neoplastic processes and carcinogenesis (including detoxification of carcinogenic metabolites) is widely reported. It has been demonstrated that smokeless tobacco extract-induced oxidative stress and apoptosis in a primary culture of human oral keratinocytes have been significantly protected by GSP and exhibited superior protection as compared to a combination of vitamins C and E. GSP exhibited potent modulatory effects of pro-apoptotic and apoptotic regulatory bcl-XL, p53, c-myc, c-JUN, JNK-1 and CD36 genes. Long-term exposure to GSP may serve as a novel chemoprotectant against three stages of DMN-induced liver carcinogenesis and tumorigenesis including initiation, promotion and progression. GSP may selectively protect against oxidative stress, genomic integrity and cell death patterns *in vivo*. The pretreatment of the animals with GSP for 7 days followed by individual exposure to amiodarone, doxorubicin and dimethylnitrosoamine in order to assess the protective ability of GSP on the amiodarone-induced pulmonary toxicity, doxorubicin-induced cardiotoxicity and dimethylnitrosamine-induced spleen toxicity have shown that GSP exhibits excellent protection in terms of serum chemistry changes and restored genomic and histopathological integrity. Amiodarone, doxorubicin and dimethylnitrosamine cause massive damage to the pulmonary, heart, spleen and brain tissues, respectively, as compared to the control animals. GSP protects against structurally diverse drug- and chemical-induced multi-organ toxicity, induces selective cytotoxicity toward human breast, lung, gastric and pancreatic cancer cells while maintaining growth and viability of normal cells. Thus a broad spectrum of studies have demonstrated that GSP prevents against DMN-induced hepatic carcinogenesis by selective preventive and cell death patterns, by modulating gene expression profiles and protecting genomic integrity.

Apoptosis is a critical defense mechanism against the formation and progression of cancer and exhibits distinct morphological and biochemical traits. Targeting apoptotic pathways becomes an intriguing strategy for the development of chemotherapeutic