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Editorial

Cancer Treatment - From Immunotherapy To Gene Therapy And Beyond

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Cancer is the oldest disease having affected humankind. Attempts to treat it have taken the shape of a "war" and have best been described in military terms. So far, despite winning some battles, we have waged that war without focus and unsuccessfully for the past 4,000 years with an accelerated campaign only during the last four decades. We rarely saw the enemy as it hid behind other diseases (cholera, dropsy, leprosy, plague, pneumonia, smallpox, and tuberculosis) and mostly affected the older populations. However, with increasing lifespan and a partial clearing of these other diseases, cancer came back in full force and roaring. From the earliest accounts dating to the Greek historian Herodotus (440 BC) within the context of breast cancer, the latest pronouncements of the World Health Organization (WHO) are that " … cancer is the second leading cause of death globally, accounting for an estimated 9.6 million deaths, or one in six deaths in 2018". For 2020, the numbers of estimated cases/deaths for the various types of organ cancers were: breast (2.26 million/685,000), colon and rectum (1.93 million/935,000), liver (830,000 deaths), lung (2.21 million/1.8 million), prostate (1.41 million), skin (non-melanoma) (1.20 million), and stomach (1.09 million/769,000). Further, for 2021, model-based projections by the American Cancer Society (ACS) predicted 1,898,160 new cases and 608,570 additional deaths in the U.S.

But, why hasn't cancer been defeated despite a seemingly intensive four-decade "war" against it and the expenditure of hundreds of billions of dollars worldwide? In my view, it is essentially because of our incomplete understanding of what I termed its 'deep biology', that is of the basic underlying molecular mechanisms that drive it. As we now understand it, cancer is a multiplicity of diseases caused by the uncontrolled growth of a single cell unleashed by mutations. Cancer cells can grow faster, flourish more profusely, adapt better, recover more rapidly, and repair faster... than normal cells. They are, in effect, more perfect versions of normal cells....and can even become immortal! Therefore, we naively thought that cancer could be defeated by either preventing mutations from occurring in normal cells or else finding the means to eliminate the mutated cells without compromising normal growth. Unfortunately, this view does not take into account the perverse genetic intertwining of normal and cancerous growths. Unbraiding the two is the most formidable undertaking.

Fortunately, more than 30% of cancer deaths are due to controllable lifestyle choices and, thus, could be prevented by avoiding risk factors (tobacco use, overweight, obesity, insufficient or/and inappropriate diet, physical inactivity, alcohol consumption, transmitted infections, and air pollution). Others are due to environmental causes that may not be controllable such as naturally-occurring background electromagnetic radiation.

Now, no less than eleven hypotheses (or theories) of cancer have so far been advanced over the years. some of which will be discussed in this Journal's issue in the context of the particular cancers that affect the brain, breasts, lungs, liver, pancreas, and genital organs, among others. Beyond the usual chemotherapeutic and surgical approaches, the major recent developments in cancer treatment will be discussed in this Journal's issue, including:

Nano chemotherapy: Nanoparticles that encapsulate one or more cytotoxic drugs are delivered at high levels to tumors. The technology has numerous clinical advantages in that the nanoparticles are non-toxic, safely metabolized, evade the immune system, and preferentially bind to damaged blood vessels and certain pathogens.

Immunotherapy (both innate and synthetic): In innate immunotherapy, postoperative malignant glioma recurrence is suppressed with neutrophil-mediated drug delivery. This process efficiently slows the recurrent growth of tumors and significantly improves the survival rates. While it does not completely inhibit the regrowth of tumors, it prolongs life significantly. In synthetic immunotherapy (the Science magazine declared it a breakthrough for year 2013), chimeric antigen receptor T-cells or programmed-death inhibitors target the immune system not the cancer itself. Unfortunately, it does not help every one (there are long odds for patients with metastatic cancer). It does, however, treat malignancies having the right error-riddled DNA signature. As an added benefit, the engineered cells continue to .protect against recurrence or re-infection for years to come

Oncogenomics: Based on the search for allgenomicsprocesses and pathways that could evidence actionable treatment indicators, it utilizes a multi-drug chemotherapeutic tool. Unfortunately, as a sequel to variouschemo therapiespatients develop resistance to drugs and therapies. The focus is on agents (e.g. viruses) and events (e.g. , mutations) that cause or facilitate genetic changes in cells destined to become cancerous, the precise nature of the genetic damage, and the genes that are affected by it. For solid tumors, immunotherapy with autologous CAR-T cells engineered to target the appropriate cancer cells is employed. In non-solid tumors, autologous CAR-T cells engineered to target RCMA (a protein on the surface of myeloma cells) did not succeed. Possible solutions are then .RNA sequencing

Oncoepiepigenomics: The manipulations of epigenetic mutations hold great promise in prevention, detection, and therapy with several epigenetic drugs already in use. These pharmaceuticals could be a replacement or adjuvant therapy for currently accepted treatment methods (radiation, chemotherapy) or could enhance their effects. Drug development has focused mainly onH istoneA cetylT ransferase (HAT) andH istoneDeacetylase (HDAC). The HDAC inhibitor Varinostat plays an integral role in the progression of oral squamous cancer. Functional epigenomics .(or the engineering of the epigenome), RNA, and beyond RNA-epigenetics are other technologies

Antiangiogenesis: The premise of this approach is to cut-off the blood vessels that aliment the cancer cells and that have been hijacked by the cancer cells to feed off them. In the case of brain cancer, this results in a weakened blood-brain barrier that may explain the rapid spread of glioblastomas. Using the barrier's weakness may help target drugs .into the brain during the early stages of the cancer

DNA Origami/Trojan technique: This technique foils drug resistance in solid tumors and works on most any form .of drug-resistant cancer

Enzyme mnk-2 conversion: This technique wherein the binary enzyme mnk-2 (the “normal” form inhibits cancer development and the “abnormal” form promotes it) also overcomes drug resistance in breast, lung, and colon cancers. Whether the cancer is arrested or promoted is determined by the balance between these two forms. Drug resistance is achieved by molecules that have been developed to convert the abnormal to the normal form of mnk-2.

Self-eradication of cancer during meiosis: This “inherent death mechanism” can self-eradicate the cancer and the more so for rapidly proliferating human cancer cells. This newly discovered mechanism (a modification of specific proteins that affect the construction and stability of the spindle) can arrest cancer cells from dividing and multiplying,

.and stop cancer progression in its track. It may be suitable in cases where traditional chemotherapy is not successful

Combating inflammation: Mediated by interleukin IL-1β, inflammation in the tumormicro-environmenthas a major role in cancer invasiveness, progression, and metastasis. Combating it through inhibition of IL-1β may be a treatment adjunct. Further, coupled with the monoclonal antibody Canakinumab, it has resulted in the reduced .incidences of fatal lung cancer

Electropermeabilization: Short and intense electric pulses transiently permeabilize the cell membrane, allowing the delivery of drugs to the cell's interior. In the case of electrochemotherapy, non- to low-permeant drugs have been delivered in the successful treatment of cutaneous and subcutaneous tumors or their metastases (melanoma, Kaposi .(sarcoma, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, and breast cancer

Nano-robotics: While still in research an development, swarms of nanorobots working fast together could perform microscopic and macroscopic tasks with nanoscale precision, especially in the case of glioblastomas. They come in two 'flavors' depending on whether or not they can replicate themselves without any constraints in the natural environment: only the latter are currently considered and utilized. Autonomous DNA nanorobots have been designed as intelligent drug delivery and therapeutic systems that respond to molecular triggers in vivo. Other autonomous .nanorobots have been programmed to shrink tumors by cutting-off their blood supply (an antiangiogenic approach)

Brachytherapy with alpha-particles irradiation: Brachytherapy is a treatment method where sealed radioactive sources deliver radiation at a short distance by interstitial, intracavitary, or surface application. A high radiation dose can be delivered locally to a tumor with rapid dose fall-off in the surrounding normal tissue. Currently, artificially-produced radionuclides are increasingly used (Cs-137, I-192, Au-198, I-125, Pd-103, more rarely Co-60). The radium-222 isotope can travel as far as 3 mm, releasing atoms that diffuse inside a tumor and emit their own α-radiation (a cascading effect). This approach has tremendous value not only in destroying the tumor but additionally preventing cancer from spreading to other organs.

Others: Other cancer theories and therapies continue to be proposed.

With the momentous advances of the Human Cancer Genome Project, understanding more intimately the deep biology of cancer, gene by gene and pathway by pathway, will direct us to other cancer therapeutics. Further, integrating our understanding of aberrant genes and pathways will better explain the behavior of cancer. A third and more obvious direction would be the prevention or/and minimization of underlying epigenetic and Eco genetic risk factors. The ultimate goal would be the personalization of the cancer treatment.

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