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International Journal of Molecular and Immuno Oncology

Editorial

Nanobytes-molecular and immuno-oncology

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Received : 07 August 2020
Accepted : 07 August 2020
Published : 08 September 2020

DOI
10.25259/IJMIO_21_2020

Quick Response Code:

"*We should not give up and we should not allow the problem to defeat us.*" – Dr. A.P.J Abdul Kalam

Today, it is a time when we are facing immeasurable challenges as a global population. In such times, it is commendable that scientific inquiry, medical care, research, and communication of clinical and basic oncology have persevered against all the odds. Here, we summarize just a few recent exciting advances in the field of molecular and immuno-oncology.

"DON'T EAT ME" SIGNALS – TARGET FOR CANCER IMMUNOTHERAPY

Cancer cells have a way of fooling our immune system and proliferate in the organism continuously by over-expressing "don't eat me" signals. Such signals are conveyed by CD47, programmed cell death ligand 1, β-2 microglobulin subunit of MHC-1, and recently discovered CD24 by the authors. Researchers observed that CD24 was expressed at high levels in tumor cells compared to the normal tissue. The role of CD24 as a "don't eat me signal" was confirmed by editing the breast cancer cell line genome, that is, by removing the gene responsible for expressing CD24. A heterogeneous population of cells – CD24 deficient cells and human macrophages was plated, and as a result, it was observed that the CD24 deficient cells were engulfed rapidly by macrophages. Later, the tumor cells expressing CD24 were treated with an antibody, Siglec-10, which not only blocked the interaction between CD24 and macrophages directly but also enhanced the ability of the macrophage to clear tumor cells. Although, the presence of antibody did not affect the CD24 deficient cells. Since CD24 levels are high in tumor cells (specifically ovarian and breast cancer cells here), researchers believe that CD24 blocking therapies should be able to clear out tumor cells without harming the healthy cells.[1]

G-QUADRUPLEXES – A POTENTIAL TARGET FOR BREAST CANCER TREATMENT

A recent study indicated that DNA structures called G-quadruplexes (G4) and rich in guanine bases formed when a single strand of double-stranded DNA loops out and doubles back on itself forming a quadruplex play an important role in breast cancer. Quadruplexes have been known to appear across the human genome, but exist in high levels in rapidly dividing cells like cancer cells. Such structures, even though common in cancer cells, have been first discovered by the authors in breast cancer cells. They have previously developed sequencing tech capable of detecting G4 which they have used to study 22 model tumors (biopsies) which were further transplanted and

grown in mice. During replication in cancer cells, some regions (specifically genes that help in tumor growth) may replicate several times resulting in copy number aberrations (CNA) and a prevalent number of G-quadruplexes which are found in CNAs. Synthetic molecules called pyridostatin and CX-5461 have been identified by the researchers which seem to target G4 resulting in the prevention of further cell division and successfully dealing with cancerous cells. Hence, G4 proves to be a potential weak spot which can be used for cancer therapy.[2]

BONE LOSS PREVENTION STRATEGIES POST-CHEMOTHERAPY/RADIATION

A recent study in journal cancer research exemplifies that cellular senescence (non-dividing living cells), which results as a response to stress such as DNA damage caused by chemotherapy and radiation, is known to cause bone loss. Previously, cellular senescence was known to play a beneficial role in blocking damaged cells from proliferating and giving rise to tumor cells. However, it is now known from mice studies presented by authors that senescent cells release molecules that disrupt bone remodeling. Bone remodeling involves osteoclast that dismantles old bones and osteoblast that build new bones, and an imbalance in the osteoblast and osteoclast cells leads to osteoporosis. Low levels of sex hormones, specifically estrogen, contribute to bone loss in females with ovarian or breast cancer. Senescent cells are generally removed by the immune system, but this is not the case when the immune system is compromised, especially with people of older age. To investigate the role of senescent cells, mice were treated with doxorubicin and paclitaxel and some received radiation in a leg. It was observed that p38MAPK-MK2 pathway regulates the expression of the proteins released by senescent cells, which was activated in bone cells. Hence, researchers focus on p38MAPK-MK2 pathway as a potential target to prevent bone loss. Inhibitory drugs for p38 MAPK protein and MK2 have significantly shown to preserve bone in the face of chemotherapy. Bone loss is a compromise with the lives of cancer survivors; hence, it is important to focus on strategies to prevent downsides of chemotherapy and radiation.[3]

DENDRITIC CELL ACTIVATION – KEY FOR IMMUNE SURVEILLANCE IN PANCREATIC CANCER

Hegde *et al*. have shown in mouse models of spontaneous pancreatic and lung cancer that there was an 80-fold lower number of active dendritic cells in pancreatic tumors than in lung tumors. However, on boosting the activity of dendritic cells using CD40 agonist combined with Flt3 ligand, they observed an increase in T cell infiltration and slowing of pancreatic tumor growth. They concluded that overcoming deficiency of dendritic cells in early-stage pancreatic adenocarcinoma led to disease restraint, while restoration of the function of dendritic cells in advanced pancreatic adenocarcinoma would enhance the responsiveness to radiation therapy, suggesting that a combination therapy with radiation would be most effective.[4]

GUT MICROBIOME FOLLOWING HEMATOPOEITIC STEM CELL TRANSPLANTATION

Using a technique known as 16S ribosomal RNA sequencing, researchers performed genomic analysis of nearly 9000 fecal samples. These samples were of 1350 people who were undergoing allogeneic stem cell transplantation across four centers New York (US), Japan, North Carolina (US), and Germany. They observed decrease in intestinal microbiome diversity following stem cell transplantation in all four centers. Diversity of intestinal microbiota at the time stem cell transplantation was associated with lower mortality.[5]

RNA SIGNATURES AND PREDICTING RESPONSE TO RAMUCIRUMAB IN GASTRIC CANCER

Ramucirumab is a monoclonal antibody that binds to vascular endothelial growth factor receptor 2 and blocks the binding of vascular endothelial growth factors A, C, and D. This, in turn, prevents the downstream signaling mediated by these growth factors and associated angiogenesis. Sorokin *et al*. showed that tumor RNA sequencing profiles for 15 advanced gastric cancer patients were linked with data on clinical response to ramucirumab or its combinations. They found that three genes, *CHRM3, LRFN1,* and *TEX15*, showed differential expression in the tumors for responders versus non-responders, of which *CHRM3* was up-regulated in the responders. *CHRM3* is a muscarinic acetylcholine receptor that is known to mediate various cellular responses, including inhibiting adenylate cyclase, breaking down phosphoinositides, and modulating potassium channels through G proteins.[6]

MOLECULAR FINGERPRINTS – DNA METHYLATION-BASED LIQUID BIOPSY PREDICTIVE OF CANCERS

Liquid biopsies are used for detection of molecular signatures in blood and other body fluids. This approach is effective in early cancer detection as well as in monitoring cancer treatment. In general, mutations are picked up in

circulating DNA or DNA fragments which have been shed from the tumor tissue. Recent studies have used DNA methylation patterns as a new and robust way of detecting cancers early. The approach uses machine learning to use DNA methylation patterns as a predictive measure for cancer. This is particularly useful for tissues that do not shed much DNA and have proven challenging for the traditional DNA mutation-based liquid biopsies such as kidney and brain.[7,8] Most remarkably, the test could predict renal cell carcinoma with high accuracy not only by assessing DNA methylation in blood but also using urine samples.[7]

A REMARKABLE RESOURCE – PAN CANCER WHOLE GENOME ANALYSIS

The sheer volume of cancer-related data is daunting to many scientists and clinicians, with an ever-growing need for transdisciplinary teamwork to derive meaningful conclusions. To this end, in a large undertaking, researchers have mapped the evolution of 38 different cancer types by evaluating data from 2658 unique donors. Cancer emergence and accumulation over time have been associated with specific genomic alterations in the international study that used whole-genome sequencing. For example, in glioblastoma, the mutations linked to cancer even occurred as early as during fetal development. In ovarian cancer, the mutations were traced to several years before the tumor development. In general, driver mutations occurred earlier in the cancer timeline. Risk and exposure molecular signatures such as UV exposure-associated in melanoma and smoking-associated with lung cancer were also observed early.[9]

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How to cite this article: Vaishnav R, Morjaria S. Nanobytes-molecular and immuno-oncology. Int J Mol Immuno Oncol 2020;5(3):89-91.