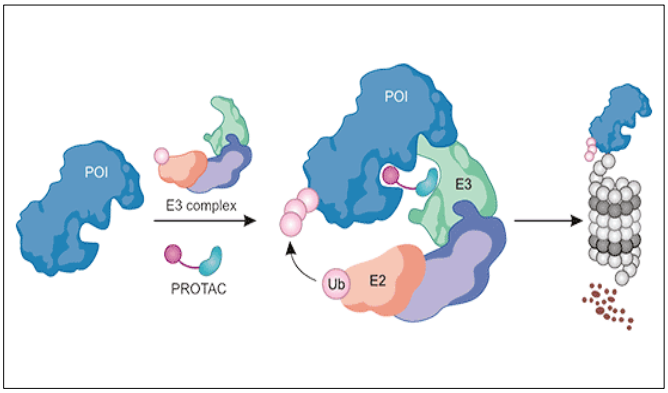
BRAC UNIVERSITY School of Pharmacy

PHARMA HIGHLIGHTS

ISSUE 99 | December 2022

Future of Proteolysis Targeting Chimera (PROTACS) in Therapeutics



The ubiquitin-proteasome system is hijacked by proteolysis-targeting chimeras (PROTACs), a promising paradigm-shifting technology, that enables targeted protein degradation. The induced closeness between an E3 ligase and POI by PROTACs causes the development of polyUb chains on substrates and subsequent proteasomal-mediated destruction of POI. The degradation of numerous disease-causing proteins, including the androgen receptor and BRD4, by PROTACs, has demonstrated their strong therapeutic potential. The repertory of PROTAC targets has greatly expanded as a result of the considerable advancements in PROTAC technology during the past two decades. A number of literature studies on PROTAC technology have proved insight into the feasibility of PROTAC technology to degrade target proteins. Additionally, the first oral PROTACs (ARV-110 and ARV-471) have shown encouraging results in clinical trials for prostate and breast cancer treatment, which inspires a greater enthusiasm for PROTAC research. In recent days, PROTAC is targeting crucial oncoproteins and unleashing new challenges in the PROTAC realm to design excellent PROTACs for targeted cancer therapy.

Proteolysis Targeting Chimera (PROTAC) can overcome most of the limitations of small molecule inhibitors, and they offer several advantages of the traditional concepts of drug discovery by targeted protein degradation. Their mode of action (MoA) suggests that a small molecule just needs a brief interaction with its target protein, leading to the loss of function of the target. After the target protein's destruction, this small-molecule drug can survive and carry on another cycle of target-protein degradation. This sub-stoichiometric activity is catalytic in nature, avoiding maintaining a high level of drug dosage. Since the POI is totally degraded by the body's own destructive system, and that the target protein must now be resynthesized after the degradation event, overexpression and accumulation of the target protein can be averted by proteolysis targeting chimera technology, leading to fewer adverse effects. In addition to this, traditional inhibition often fails to address the conformational changes in proteins due to mutations, thus causing increased drug resistance, which is easily addressed by the PROTAC approach, where the intense-target binding is often not required to the unique MoA. Therefore, this approach also has the potential to target the "undruggable" proteome that limits traditional drugs, as the warhead needs only a slight binding affinity to recruit the protein of interest (POI) rather than high inhibition activity.

Classical drugs generally require high drug concentrations to maintain a level of target occupancy that provides sufficient clinical benefit. However, high drug concentrations are also linked to off-target effects. Since the PROTAC efficacy is not limited by equilibrium occupancy, a reduction in protein levels of more than 90% can be reached at nanomolar concentrations. In addition, they promise a more sustained reduction in downstream signaling and the maintenance of response duration even after washout of the PROTAC. In contrast to a typical interaction of an inhibitor with the target protein where the inhibitor is required to bind to a functional binding site and block a single protein interaction, PROTACs result in a ternary complex in which recognition is crucial, whereas potency is of reduced significance. This makes PROTACs more suitable for 'difficult' targets, where the known inhibitors are typically a failure due to weak binding and are unsuitable for further clinical development or for protein-protein interactions.
Therefore, systematic exploration and evaluation of PROTAC delivery systems would also be valuable for other protein degraders.

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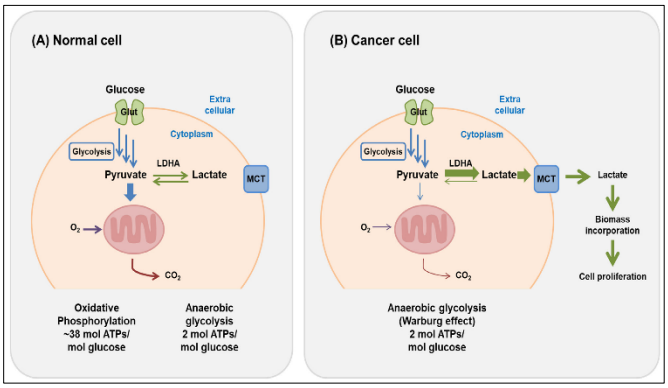
Warburg Effect: Association of Cancer with Type II Diabetes



“Cancer and diabetes are the two sides of the same coin," asserted Debbie Thurmond, Ph.D., chairman of the Department of Molecular & Cellular Endocrinology at the Diabetes & Metabolism Research Institute at the City of Hope. He also added, "They are disruptions of the body's normal metabolism."

A common illness known as type 2 diabetes raises the blood sugar (glucose) level too high. It may result in symptoms including extreme thirst, frequent urination, and fatigue. It may also make a patient more susceptible to significant heart, nerve, and eye issues. Liver and pancreatic cancer are twice as likely in those with type 2 diabetes. It is evident that cancer and diabetes are closely connected in many aspects, from risk factors to therapeutic efficacies.

Additionally, a condition may exacerbate another. According to a few researches, type 2 diabetes characteristic extremely high insulin levels may contribute to cancer. Some cancer cells are simultaneously waiting for blood sugar levels to increase. Cancer cells love glucose, and it's their primary fuel; it was proved in 1930 when the Warburg Effect was introduced. Otto Warburg, a Nobel Prize winner, proved that cancer cells absorb and consume glucose 200 times higher than usual. In reality, positron emission tomography scans are intended to find regions of the body that use a significant amount of glucose to discover the existence of cancer there. Cancer cells rearrange their metabolism to support growth, survival, proliferation, and long-term maintenance. The increased absorption of glucose and the fermentation of glucose to lactate are frequent characteristics of this altered metabolism.

The Warburg Effect refers to this phenomenon, which can be seen even when the mitochondria are fully functional. Even in the presence of oxygen and completely functional mitochondria, the rate of glucose absorption increases, and lactate is produced preferentially, according to the definition of the Warburg Effect.

The Warburg effect is a finding in oncology that most cancer cells primarily produce energy through 'aerobic glycolysis,' which involves high levels of glucose uptake and glycolysis is followed by lactic acid fermentation occurring in the cytosol rather than the mitochondria, and also in the presence of abundant oxygen. This process is less efficient than the 'usual' citric acidcycle and oxidative phosphorylation in mitochondria, as observed in normal cells. Energy may be obtained from ATP by oxidizing the carbon bonds in the critical macronutrient glucose during metabolism. It is through this procedure that all mammalian life is sustained. In animals, the final byproduct may be lactate or, after the complete oxidation of glucose via mitochondrial respiration, CO2. The glucose uptake rate dramatically increases in tumors and other dividing or developing cells, producing lactate.

After smoking and obesity, type 2 diabetes mellitus is most likely the third modifiable risk factor for pancreatic cancer. Long-term type 2 diabetes mellitus has been linked to a 1.5–2.0-fold increase in the incidence of pancreatic cancer, according to epidemiological studies. In prospective trials, results from prediagnostic assessments of glucose and insulin levels also show a causal connection between diabetes and pancreatic cancer. The fundamental processes for developing diabetes-related pancreatic cancer have been hypothesized to include insulin resistance and related hyperglycemia, hyperinsulinemia, and inflammation. Cell proliferation and tumor development are significantly influenced by signaling pathways controlling the metabolic process. There are currently no reliable clinical or scientific ways to pinpoint the onset of a disease or tell type II diabetes from diabetes brought on by pancreatic cancer. Most malignancies have lengthy latency periods, and many cases of prediabetes and diabetes go untreated before the malignancy is diagnosed.

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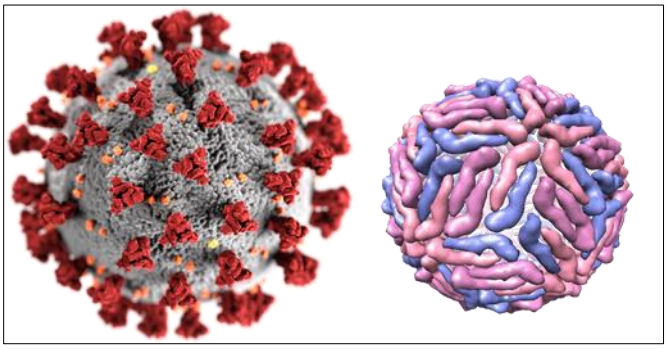
Dengue And Covid-19: They Work Closer Than You Might Think



Dengue virus (DENV) and SARS-COV-2 are two viruses that causes viral infections in humans which is useful to study for their immunopathogenesis and derive clinical methods accordingly for therapy. Although their way of entry is different, both result in systemic infection with similar clinical manifestations such as fever, gastrointestinal diseases, and microthrombi. Moreover, both infections are characterized by an impaired type I-IFN response and a proinflammatory immune response because of similar types of cytokines and chemokines are elevated in both dengue and COVID-19 similarly, both viruses are characterized by lymphopenia. Lymphopenia has been shown to correlate with clinical disease severity. The lymphopenia in dengue is mostly due to reduction in T-cells due to apoptosis. While lymphopenia in COVID-19 is mainly due to reduction CD8+ T cells. The risk factors are also heavily similar proven with fact that the observable correlation especially mortality rate between the two viral infection is significantly detected by old age, pregnancy , and comorbidities such as diabetes , hypertension ,obesity , asthma , chronic kidney diseases. Also, both DENV and SARS-COV-2 infect many type of immune cells such as monocytes, dendritic cells, mast cells, hepatocytes, kupffer cells, alveolar macrophages, and macrophage like cells in the lymph nodes and spleen and many organs in the body, leading to a widespread infection. Similar to the observations in dengue, although with little evidence, endothelium dysfunction plays a significant role in the pathogenesis of COVID-19. Common cellular changes in hematological parameters in dengue and COVID-19 are due to decrease in CDK 4, CDK 8, CDK 3 and an increase in platelet levels. Antibody and B-cell responses in patients with severe dengue and COVID-19 are caused by highly potent neutralizing antibodies, heightened plasmablast and extrafollicular B cell responses, antibody development enhancement, and autoantibodies. In conclusion, since the initial clinical manifestations of these two infections are quite similar, it would be a challenge to clinically differentiate these two infections.

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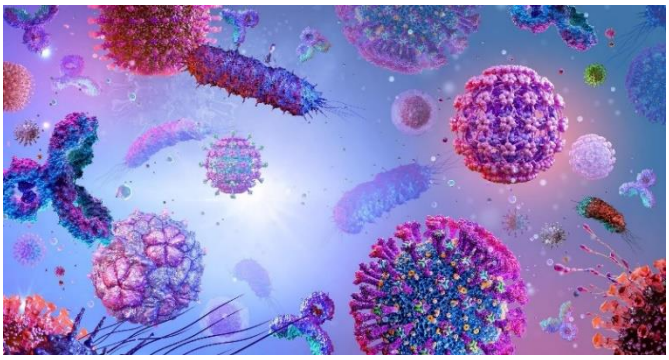
Bacteria are Ubiquitous: The Large Effect of Small Inhabitants

Bacteria have a poor reputation. It seems to make sense that many people link microorganisms to sickness. Although harmful bacteria that cause disease typically receive the most attention, bacteria really have numerous positive effects on both the environment and humans.



Bacteria are crucial to the world, but they are also an essential component of ourselves. Every part of the human body, including the internal gastrointestinal system and the exterior skin, is covered in bacteria. Even the eye's microbiome is the subject of several investigations. Bacteria have traditionally been studied by "culturing" them, or cultivating them in test tubes and petri dishes to define their metabolism and comprehend their roles. The issue with this strategy is that most bacteria are extremely challenging to cultivate in a lab setting. Some bacteria are adapted to particularly particular settings that researchers can't always replicate in a laboratory. The development of molecular biology, and particularly the capacity to sequence DNA, fundamentally altered how researchers study They are the workhorses of the planet, sustaining much of the world's plants by fixing nitrogen (think of it as making fertilizers out of thin air) and carrying out photosynthesis in the oceans. They likely account for a greater portion of the world's population.

microorganisms. Without needing to cultivate every type of bacterium, researchers were able to identify some of them by sequencing the DNA of a sample taken from the environment. Only a small number of sequences could be effectively retrieved during the early stages of sequencing since it was such a labor-intensive operation. Recent technological advancements have made it possible to sequence DNA at dizzyingly fast rates at drastically lower costs, allowing scientists to finally view practically all of the species that make up the community, not just a tiny portion. The Human Microbiome Project was started in large part due to this development. “A logical extension of the Human Genome Project," is how some people have described the Human Microbiome Project. In the body, bacterial cells outnumber human cells 10 to 1, hence it is believed that they are crucial to maintaining human health. For instance, the health of our digestive system depends greatly on microorganisms. Scientists now understand that both fat and thin individuals have various bacterial species. The investigators however, discovered that the bacterial populations observed in lean vs obese people varied significantly. Another research employed mice as a model organism, despite the fact that it did not establish a causal connection in humans. The scientists proved that the microbiome regulates the amount of fat accumulation regardless of diet by transplanting the microbiome of obese mice into thin animals. This effect is obvious when you realize that the majority of nutrients we intake are broken down by both the bacteria that line our intestines and human enzymes. Bacteria are always present in our life. Although it is true that germs may lead to disease, they also support our overall health. Scientists are now understanding how the intricate bacterial ecosystems in our bodies affect our health thanks to the Human Microbiome Project. The HMP may lead to novel therapies and treatments for numerous ailments as a result of new technology. One notable instance is the use of gut microbiota transplant to treat Clostridium difficile infections. Instead of eradicating the ‘bad’ bacteria, new treatments could concentrate on promoting the growth of the ‘good’ bacteria.

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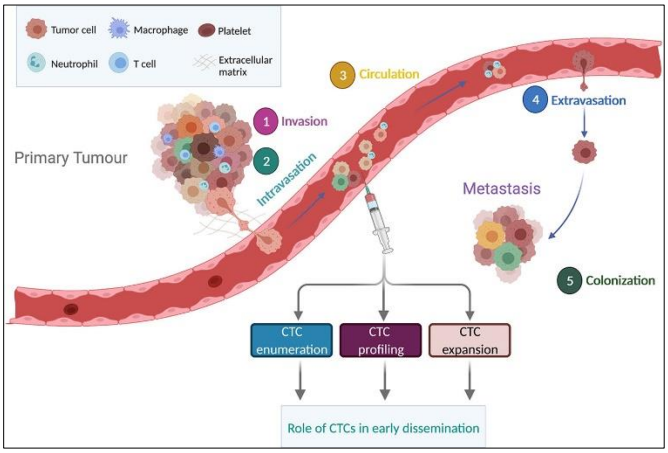
Circulating Tumor Cells (CTCs) as Biomarkers in Early Cancer Detection

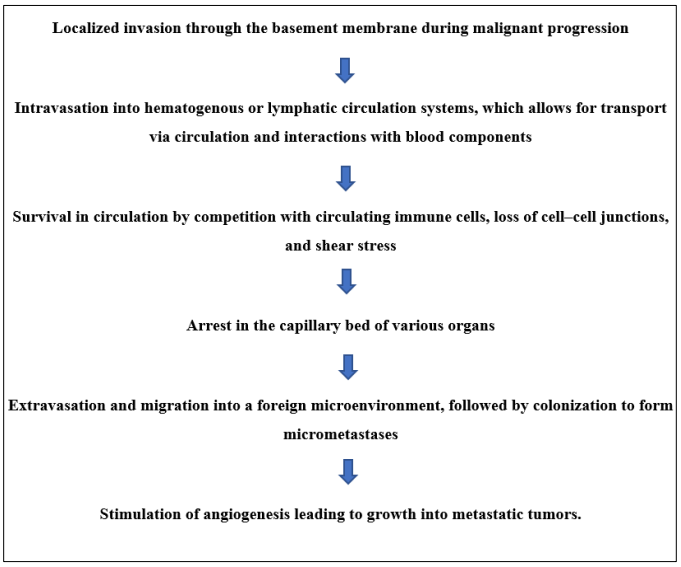


Circulating tumor cells (CTCs) are cancer cells that escape from the main tumor and spread throughout the body through the peripheral blood circulation system. Clinical uses for circulating tumor cells include cancer cell genetic profiling and tracking the development or recurrence of the disease. Through liquid biopsy, sensitive CTC detection from clinical samples can be a useful tool for determining the prognosis and diagnosis of cancer.

Due to tumor heterogeneity, current CTC detection technologies primarily rely on biomarker-mediated platforms like magnetic beads, microfluidic chips, or size-sensitive microfiltration, which might reduce detection sensitivity. With the surface-charged superparamagnetic nanoprobe, a more sensitive, biomarker-independent CTC separation approach has recently been created, capable of capturing several EMT subpopulation CTCs from 1mL of clinical blood. Comparatively speaking to conventional tissue biopsies, this approach is relatively benign because circulating tumor cells are often acquired through a blood sample.

According to numerous recent studies, clinicians treating specific forms of breast cancer could choose between chemotherapy and endocrine therapy based on the number of circulating tumor cells. When compared to the doctor's choice of treatment, using circulating tumor cell (CTC) count to select between first-line therapies improved overall survival for patients with metastatic, estrogen receptor (ER) positive/HER2-negative breast cancer.

Tumor cell dissemination may occur in the following steps:



Scientists proposed that the CTC count might influence and standardize the challenging choice of treatment between chemotherapy and endocrine therapy, which may be more advantageous for patients with poor prognoses. The general agreement among experts is to explore all endocrine therapy options before switching to chemotherapy because they often have fewer negative effects than chemotherapy. Doctors and treatment facilities make very different treatment recommendations despite the general agreement.

As one of the important markers of tumor liquid biopsy, CTCs have been recognized to provide valuable information in both fundamental cancer biology studies and clinical diagnosis and prognosis. For phenotypic analysis, single cell biological characterization, and nano-bio interface studies, which are crucial for both basic cancer biology research and downstream applications, consistent and effective capture of CTCs is urgently needed. In light of this, the following crucial concerns must be included in future clinical research: (1) Create clinically viable CTC isolation techniques that address certain liquid biopsy requirements, (2) focus on diseases that haven't received enough attention, such head and neck cancer, (3) require more effective and simple approaches to locate CTCs without compromising their cellular viability, (4) using more sophisticated methods for CTC ex vivo culture.

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