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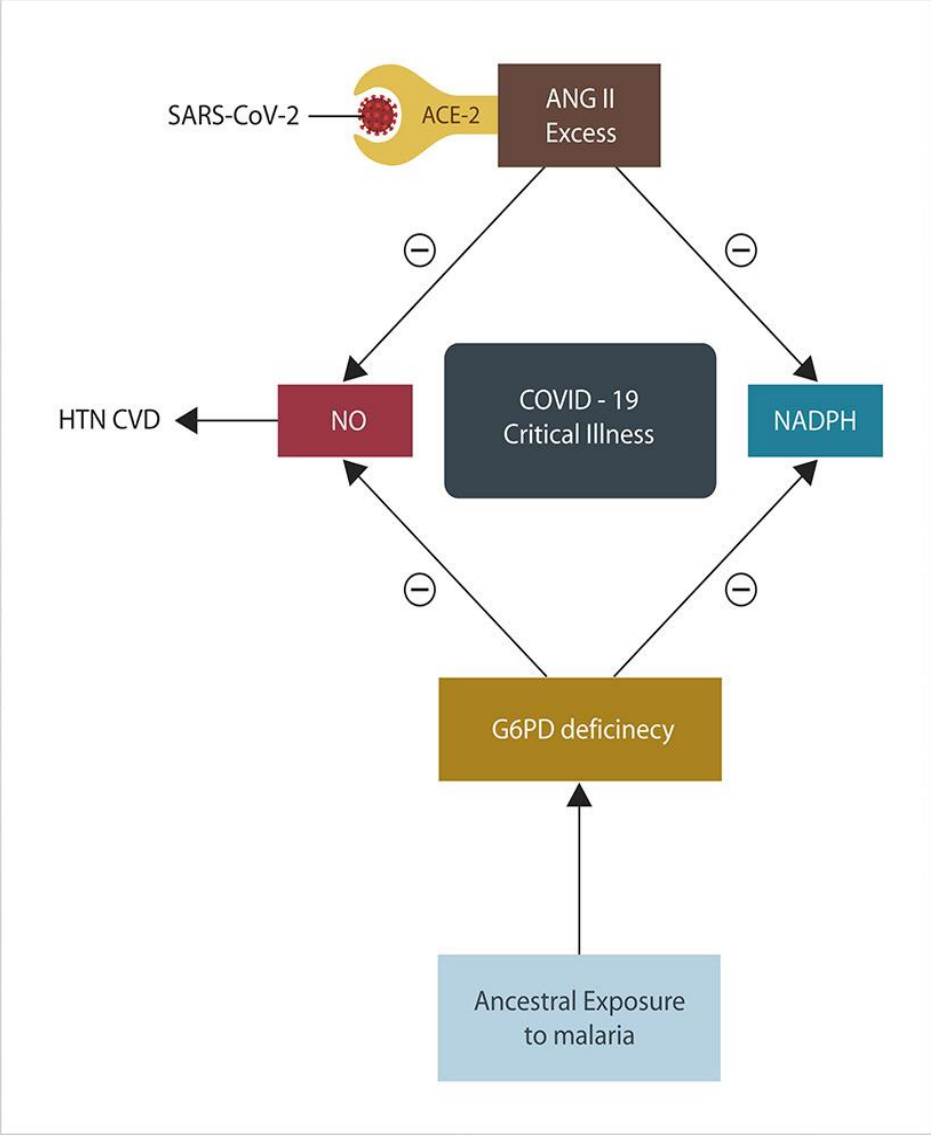

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From the Publisher's Desk

Welcome to Biotechnology Kiosk!

The October, 2020 issue of BK is now online for our readers with the regular features.

This issue contains news and views on the current cutting-edge topics that include latest research breakthroughs in Parkinson's disease and gene therapy. A mini perspective on oil degrading bacteria and the bio remedial actions to counter environmental pollution is also presented for our readers.

We look forward to receiving your feedback. We do hope that you will enjoy reading this issue of Biotechnology Kiosk. Please do write to us with your comments. Your suggestions are always appreciated.

Dr. Megha Agrawal & Dr. Shyamasri Biswas.

Co Editors-in-Chief, Biotechnology Kiosk

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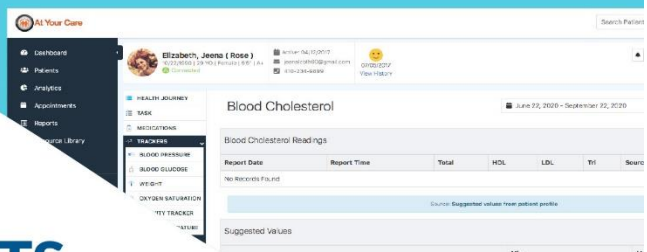

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Perspective

Oil Degrading Bacteria: Remediation of Environmental Pollution Resulting from Petroleum Hydrocarbons

Ishita Agrawal*

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Abstract

It is widely known that petroleum hydrocarbons constitute one of the most hazardous pollutants that affect human and environmental health. The ongoing research on bioremediation with petroleum hydrocarbon-degrading bacteria has shown tremendous promise of the technology due to its advantages of high efficiency and eco-friendly nature. To this end, studies have been carried out to identify a large amount of bacterial species with petroleum hydrocarbon-degrading ability for applications in bioremediation. Here, we present a brief perspective of some of the notable advances in oil degrading bacteria and the remedial actions for decontamination of water and soil along with recovering the spilled materials at oil sites.

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Introduction

Petroleum oil is recognized as an important strategic resource for nearly all countries in the world. It is commonly believed that the flourishing of the petrochemical industry is reliant on the anthropogenic activity and its energy demands. However, this comes with the growing concern of environmental pollution resulting from petroleum hydrocarbons with the rapidly rising population and modernization of our society. Research studies have suggested that the use of petroleum can result in environmental deterioration. For example, it is of major concern of oil spills from pipelines to tankers and their impact on the environment. These environmental disasters require very challenging decontamination efforts with massive investments of time and resources [1, 2]. This has accelerated the demand for remediation technologies to be developed that can mitigate the environmental pollution crisis.

There are several steps involved during petroleum production that involve storage and transportation, refining and processing. These steps often involve spills and discharges of petroleum hydrocarbons that occur as a result of blowout accidents during oilfield development. These accidents can happen as a result of leakage from oil pipelines and storage tanks, oil tanker and tanker leakage accidents, oil well waxing, and also during overhauls of refineries and petrochemical production equipment [3]. The available industrial techniques allow recycling or elimination of large spills to some extent. However, it is often very challenging to recover the spilled materials that remain in the affected area. This results in persistent risks to the environment [3].

Conventional microbial remediation technology has been employed for overcoming the challenge of petroleum hydrocarbons induced pollution. However, its practical application is hindered by many environmental factors that limit the large-scale application of the technology [1]. Therefore, while oil pollution is difficult to treat, researchers have focused on improvement of microbial remediation technology for developing a new method for the remediation of petroleum hydrocarbon pollution [4]. One such area is hydrocarbon-degrading bacteria that has attracted a great deal of attention. Researchers have studied such petroleum hydrocarbon-degrading bacteria that are found in nature for the bioremediation of petroleum oil-contaminated environments. They have found these organisms as promising candidates for the treatment of oil pollutants. To this end, bacteria have been screened and utilized to degrade waste products produced by the food, agricultural, chemical and pharmaceutical industries. The use of such bacteria to deal with environmental pollutants is considered a promising technology due to its low cost and eco-friendly nature [5].

Bacteria Induced Biodegradation of Hydrocarbons

Studies have shown that bacterial surface properties are essential to the effective biodegradation of hydrophobic hydrocarbon substrates (Figure 2) [1]. Additionally, the adhesion mechanisms of these substrates are considered very important. This is due to

the fact that adherence of hydrophobic pollutants to bacterial cells is enabled by hydrophobic fimbriae, fibrils, outer-membrane proteins and lipids along with small molecules that are present in cell surfaces such as gramicidin S and prodigiosin [6].

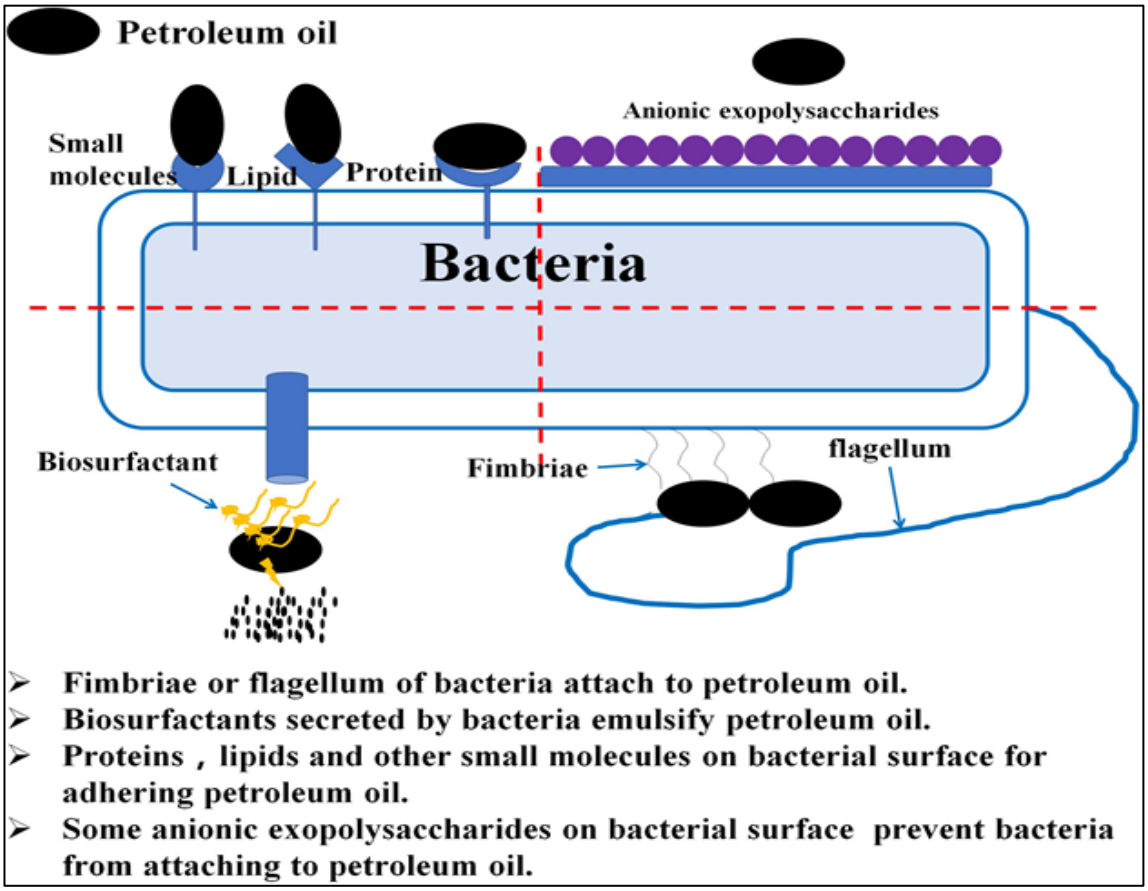

Figure 1: Schematic depiction of the mechanism of physical contact between bacteria and petroleum hydrocarbons [Source: Front. Microbiol. (2018)].

Researchers have employed a promising approach based on the application of surfactants to enhance the bioavailability of petroleum hydrocarbons. This approach is considered useful to enhance dissolution or desorption rates leading to the solubilization or emulsification of petroleum hydrocarbon pollutants [7]. Researchers emphasized on the selection of appropriate surfactants for pollution remediation and the prevention of secondary pollution [1]. For example, bioemulsifier-producing bacteria have been studied that have exhibited important physiological attributes. These include enhanced complexation and solubilization properties of non-polar substrates that promote the bioavailability. Bioemulsifier-producing bacteria also have superior affinity between cell surfaces and oil-water interfaces through metabolism that can

promote deformation of the oil-water interface film [8].

In another study, researchers demonstrated an innovative approach based on a bacterium Alcanivorax borkumensis that was shown to feed on petroleum hydrocarbons. In this approach of bioremediation for degradation of hydrocarbons, enzymes were shown to be produced by the bacterium and their effectiveness was shown in degrading petroleum products in soil and water (Figure 2). These results pave the way for new breakthroughs for a simple, effective and eco-friendly technology for decontamination of water and soil at oil sites [9].

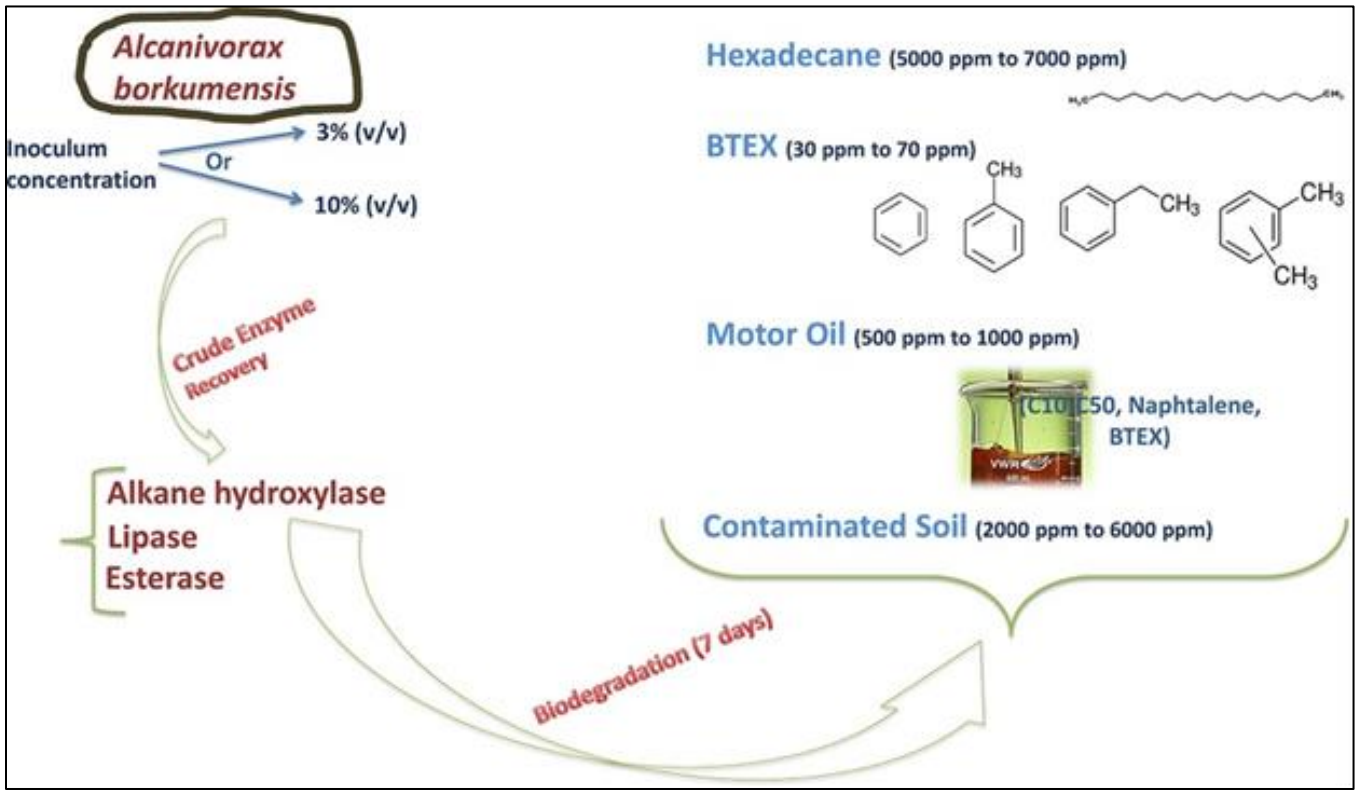

Figure 2: Schematic presentation of the biodegradation pathways by hydrocarbon-degrading bacterium with higher enzymatic capacities [Source: Biochemical Engineering Journal (2018)].

In this study, researchers used *Alcanivorax borkumensis* crude enzyme preparation as an agent for enhanced microbial hydrocarbons biodegradation in contaminated water and soil. This study confirmed the remarkable effect on the biodegradation with the crude enzymes by the inoculum and hydrocarbons concentration. Researchers showed the high enzymatic production reaching 145.71 U/mg for alkane hydroxylase, 3628.57 U/mg for lipase and 2200 U/mg for esterase. This subsequently led to a significant degradation efficiency of the different concentrations of petroleum hydrocarbon substrates reaching 73.75% for 5000 ppm of hexadecane, 82.80% for 1000 ppm of motor oil, 64.70% for 70 ppm of BTEX and 88.52% for 6000 ppm of

contaminated soil. These results suggested that *Alcanivorax borkumensis* could be a potential hydrocarbon-degrading bacterium with higher enzymatic capacities for bioremediation of hydrocarbon-polluted environment [9].

Concluding Remarks

Bacteria enabled bioremediation of petroleum hydrocarbon induced pollution is an active area of research due to its huge impact on the human and environmental health. It is anticipated that future studies will continue to focus on the theoretical aspects of the interfacial interaction mechanism between bacteria and petroleum hydrocarbons. Development of novel biocompatible surfactants is another research area that is expected to focus on new surfactant technologies to enhance contact between bacteria and petroleum hydrocarbons. In addition, new biotechnology routes can be explored to find new resources of petroleum hydrocarbon-degrading bacteria especially using high-throughput screening method to increase and enrich functional bacterial resources.

Acknowledgement

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Short Communication

COVID-19 reveals redox vulnerabilities in two minority groups

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Abstract

The COVID-19 pandemic spread rapidly throughout the world, but some populations were more affected than others. For example, compared to other groups, a higher morbidity and mortality was documented in African Americans and individuals of Mediterranean descent. These populations are marked by both increased prevalence of glucose-6-phosphate dehydrogenase (G6PD) deficiency, and lower utilization of angiotensin receptor blockers/angiotensin converting enzyme inhibitors in the treatment of hypertension. In this brief report, we suggest that G6PD status should be assessed in all COVID-19 positive individuals belonging to the two ethnic groups. If detected, N-acetylcysteine should be utilized to lower the oxidative burden and "sartans" should be prescribed as first-line therapy in hypertensive individuals.

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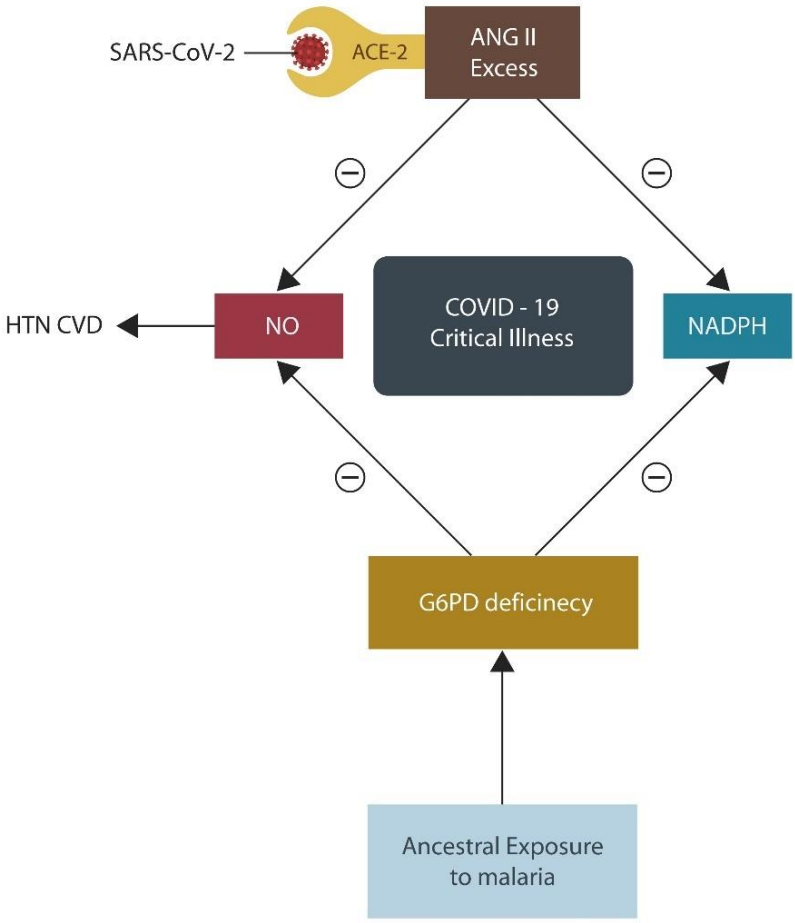
Visual Abstract



The SARS-CoV-2 virus engagement of angiotensin-converting enzyme 2 (ACE-2) impairs angiotensin II (ANG II) processing, leading to its accumulation. Excessive ANG II inhibits endothelial nitric oxide (NO) and nicotinamide-adenine dinucleotide phosphate (NADPH), increasing oxidative stress. Lowered NO, exacerbates hypertension (HTN) and cardiovascular disease (CVD), increasing the susceptibility to COVID-19 complications. Populations with ancestral exposure to malaria, including African Americans and individuals of Mediterranean descent, present with high rates of glucose-6-phosphate dehydrogenase (G6PD) deficiency, a defect that also lowers NO and NADPH, increasing the vulnerability to COVID-19. Together, the SARS-CoV-2 infection and G6PD deficiency likely generate a catastrophic redox failure, engendering COVID-19 critical illness. "Sartans" inhibit ANG II, restoring redox homeostasis (not shown).

Introduction

On March 11, 2020 the World Health Organization declared COVID-19 a pandemic. At that time, the virus had been detected in 114 countries, and 4,291 people had lost their lives. Despite its rapid spread around the globe, individuals and populations have not been equally affected. For example, it is still unclear why older persons, African Americans and people from the Mediterranean basin have been more impacted compared to other groups. Indeed, a new study found that the SARS-CoV-2 fatality rate was 2.4 times higher in African Americans compared to Whites, Asians or Latinos, suggesting a probable racial vulnerability (1). This is further substantiated by the fact that other countries with a predominantly black population reported similar data (2). In addition, mortality rates comparable to those of African Americans have been documented in individuals from the Mediterranean basin, a region where G6PD deficiency is more common than in the rest of Europe (3).

Socioeconomic conditions likely play a major role in COVID-19 prognosis, however biological factors, including the management of hypertension and oxidative stress may be equally important. We surmise that, aside from healthcare inequalities, two modifiable risk factors may contribute to the higher COVID-19 morbidity and mortality in African Americans and Europeans of Mediterranean descent:

1) lower utilization of angiotensin receptor blockers (ARBs) and angiotensin converting enzyme inhibitors (ACEi) in the treatment of hypertension, and

2) higher oxidative stress due to increased prevalence of glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Hypertension treatment practices

European hypertension studies have demonstrated that, compared to the Northern part of the continent, ARBs and ACEi are less often prescribed in the South (4). With the same token, in the US, African Americans are less likely to receive ARBs and ACEi as first line hypertension treatment (5). This prescription practice reflects the belief that the response to these drugs is hindered by the lower renin levels, demonstrated in this population. However, numerous clinical trials have found that ARBs and ACEi are equally efficacious in Black Americans and recommended that clinicians should use these agents as first line therapy (5-6). This data is significant as both ARBs and ACEi appear to lower the COVID-19 mortality rates. For example, a novel study found that patients treated with these drugs at the time of infection with the SARS-CoV-2 virus demonstrated a lower mortality rate of 30.4% compared to 41.2 % in individuals without prior exposure to ACEi or ARBs (7).

In our previous work, we found a positive correlation between COVID-19 critical illness and excessive angiotensin II (ANG II) and stated that “sartans” should be used early in the disease course (8-9). We based this assertion on the fact that ANG II upregulates oxidative stress, while ARBs and ACEi restore the redox homeostasis by lowering ANG II.

The oxidative burden

Oxidative stress is an established hypertension risk factor and several antihypertensive drugs lower the blood pressure by acting as antioxidants (10). For example, ARBs and ACEi decrease reactive oxygen species (ROS) by upregulating both endothelial nitric oxide (NO) and the master antioxidant glutathione (GSH) (11-13). As a major product of the normal endothelium, NO acts as a vasodilator and regulator of oxygen supply by its action on the smooth muscle of blood vessels. African Americans synthesize 2 to 3 times less NO compared to the general population, placing this group at higher risk of redox dysfunction, hypertension and cardiovascular disease (14-17).

Aside from decreased NO, African Americans (even after adjustment for most variables) display lower GSH plasma levels compared to other groups (18). Indeed, decreased GSH in this population was also associated with a higher incidence of prostate cancer, suggesting that ARBs and ACEi may be protective as they lower oxidative stress (19-20) (11-13).

Taken together, the SARS-CoV-2 virus alters the body redox systems by inhibiting ANG II hydrolysis, increasing oxidative stress. This may prove catastrophic in individuals or populations with preexistent redox defects, such as those described in malaria-exposed groups (see the next section). In addition, underutilization of ARBs and ACEi as antihypertensive treatments in this population, further disrupts the redox homeostasis, increasing COVID-19 morbidity and mortality.

Ancestral malaria and oxidative stress

Malaria is an old enemy of mankind that throughout many centuries exacted a heavy mortality toll on the population of Africa and the surrounding regions, including the Mediterranean basin. In response, the residents of these areas gradually developed plasmodium-resistant red blood cell phenotypes, including glucose-6-phosphate dehydrogenase (G6PD) deficiency, α+ thalassemia, and hemoglobin C (21). Although protective against malaria, these genetic variants increased oxidative stress, contributing to other pathologies, such as cancer, cardiovascular disease and neuropsychiatric disorders (22-26). Novel data links G6PD deficiency to COVID-19 complications, suggesting that populations with ancestral malaria exposure are at increased risk of critical illness. Indeed, the US Army statistics estimate that 12.2% of African American males and 4.1% of females present with G6PD deficiency, connecting the oxidative stress in this group to unfavorable COVID-19 prognosis (27).

G6PD is the rate-limiting enzyme that catalyzes the conversion of NADP to NADPH, preventing GSH depletion (28). Therefore, deficient G6PD contributes to ROS accumulation, a pathology described in severely ill COVID-19 patients (29-30). In addition, G6PD deficiency is also associated with chronically depleted NO, predisposing to hypertension, cardiovascular disease and coagulopathies, conditions prevalent in many African Americans (31). For this reason, G6PD status should be assessed in all COVID-19 positive individuals, especially those belonging to the two ethnic groups.

Moreover, as N-acetylcysteine (NAC) is an FDA approved drug and an established GSH enhancer, it should be routinely utilized in African Americans and southern Europeans with COVID-19 (32). Indeed, NAC is currently in clinical trials for COVID-19, emphasizing further the importance of redox dysfunctions in this viral infection (NCT04792021).

Future directions

Older individuals are more susceptible to COVID-19 complications and respond less well to vaccines, therefore the development of new treatments for SARS-CoV-2 critical illness should never be abandoned (34).

Further studies are needed to determine whether COVID-19 morbidity and mortality can be lowered by the routine assessment of G6PD status and utilization of ARBs and ACEi as first line therapy for hypertension in susceptible populations.

Conclusion

African Americans and people of Mediterranean descent present with a higher prevalence of hypertension and cardiovascular disease, along with an increased risk of COVID-19 critical illness.

Aside from the healthcare disparities, biological factors likely predispose these populations to oxidative stress and SARS-CoV-2 complications. Indeed, increased prevalence of G6PD deficiency and the less frequent use of ARBs and ACEi in the treatment of hypertension can explain the higher mortality rates demonstrated in African Americans and southern Europeans. As these are modifiable risk factors, screening for G6PD deficiency and adjusting hypertension treatments could save lives.

Clinicians should also be mindful that individuals with G6PD deficiency may be more prone to COVID-19-related thromboembolic events and that several commonly used therapeutics, including aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), quinolones, nitrofurantoin and hydroxychloroquine can exacerbate this pathology (33). For this reason, the above drugs should probably be avoided in G6PD deficient patients with COVID-19.

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Biotechnology Advances around the World

Editor's Picks

Every issue of Biotechnology Kiosk presents select latest research news picked by the editors-in-chief on significant research breakthroughs in different areas of biotechnology around the world. The aim is to promote further R&D in all of these cutting-edge areas of biotechnology. The editors have compiled and included the following innovations and breakthroughs to highlight the latest biotechnology advances.

Dr. Megha Agrawal
Co Editor-in-Chief

Dr. Shyamasri Biswas
Co Editor-in-Chief

Gene Therapy

Designer cytokine to cure paralyzed mice

Spinal cord injuries are considered very devastating medical condition that can be caused by sports or traffic accidents. Such injuries often result in permanent disabilities such as paraplegia, which is caused by damage to nerve fibers that are called axons that carry information from the brain to the muscles and back from the skin and muscles. This communication mechanism gets interrupted in the event of fibers getting damaged due to injury or illness. This is a very serious medical condition due to the fact that severed axons in the spinal cord can't grow back and a as result, the patients suffer from paralysis and numbness for life. Unfortunately, there is no cure or treatment option available that could restore the lost functions in affected patients.

A research team in Germany for the first-time used gene therapy to successfully getting mice to walk again after a complete cross-sectional injury. In their study, they showed the nerve cells produced the curative protein themselves and transneuronal delivery of hyper-interleukin-6 enabled functional recovery after severe spinal cord injury in mice. This work was reported in Nature Communications (Transneuronal delivery of hyper-interleukin-6 enables functional recovery after severe spinal cord injury in mice, Nature Communications, 2021; 12 (1) DOI: 10.1038/s41467-020-20112-4). Researchers demonstrated a new therapeutic approach in getting paralyzed mice to walk again. Their approach is based on the protein hyper-interleukin-6 that can stimulate nerve cells to regenerate, and the way it is supplied to the animals.

In their search for potential therapeutic approaches, researchers designed and worked with the protein hyper-interleukin-6, the so-called designer cytokine. They called it designer cytokine because it was not derived from nature and instead it was produced using genetic engineering. In this study, they induced nerve cells of the motor-sensory cortex to produce hyper-Interleukin-6 themselves. In this process, they used viruses suitable for gene therapy that was subsequently injected into an easily accessible brain area. The viruses then delivered the blueprint for the production of the protein to specific nerve cells that are called motoneurons. These cells are important because they are also linked via axonal side branches to other nerve cells in other brain areas that are required for movement processes such as walking. Researchers then transported hyper-interleukin-6 directly to these otherwise difficult-to-access essential nerve cells and released there in a controlled manner.

This approach resulted in gene therapy treatment of a few nerve cells that stimulated the axonal regeneration of various nerve cells in the brain and several motor tracts in the spinal cord simultaneously. Subsequently, it was shown that the process enabled the previously paralyzed animals that received this treatment to start walking after two to three weeks that had never been

shown to be possible before after full paraplegia.

This research paves the way for further breakthroughs in optimizing the administration of hyper-Interleukin-6 further and achieve additional functional improvements. It also includes the possibility to explore whether hyper-interleukin-6 can still have positive effects in mice, even if the injury occurred several weeks previously, which can be relevant for application in humans.

Parkinson's Disease

Tomatoes offer affordable source of L-DOPA drug to battle against Parkinson's disease

Parkinson's disease (PD) is considered to be a growing problem in developing as well as developed countries. L-DOPA is an amino acid precursor of the neuro-chemical dopamine, which is used to compensate for the depleted supply of dopamine in Parkinson's disease patients. L-DOPA is considered as the gold standard therapy for PD, which is one of the essential medicines declared by the World Health Organization (WHO), and its market value is in the hundreds of billions of dollars. However, the challenge is that in many low-income countries, it is very difficult for many people to afford the daily $2 price of synthetic L-DOPA.

Chemical synthesis route is usually employed to produce the most common form of the drug L-DOPA. Some studies have indicated that natural sources are also available for extracting L-DOPA. However, only a few plants, mostly in seeds have been reported to contain measurable quantities of the L-DOPA. In this regard, the velvet bean, Mucuna pruriens is the most studied one, which has been shown to contain up to 10% L-DOPA in its seeds. However, the challenge using this bean is the fact that the plant is covered in urticating hairs that contain mucunian, which can cause irritation and allergic reactions in field workers that harvest the crop. Additionally, it has been reported that the beans can cause elevated levels of tryptamines, which can result in hallucinations in PD patients.

Now, the scientists have overcome this problem by producing a tomato that is enriched in the PD drug L-DOPA. It is thought to potentially become a new, affordable source of one of the world's essential medicines. Their research was recently reported in Metabolic Engineering (Metabolic engineering of tomato fruit enriched in L-DOPA. *Metabolic Engineering*, 2020; DOI: 10.1016/j.ymben.2020.11.011).

Researchers showed the development of the genetically modified (GM) tomato that could have important implications for developing nations. This study on the novel use of tomato plants as a natural source of L-DOPA shows other potential benefits for people who suffer adverse effects, for example, nausea and behavioral complications that occur as a result of chemically synthesized L-DOPA.

Researchers produced L-DOPA from tyrosine, an amino acid found in many foods. They subsequently inserted a gene encoding a tyrosinase, an enzyme that used tyrosine to build molecules such as L-DOPA. Subsequently, the level of L-DOPA was observed to be elevated specifically in the fruit part of the plant that led to higher yields than those associated with L-DOPA production in the whole plant.

Researchers demonstrated the levels achieved in the tomato fruit of about 150mg of L-DOPA per kg of tomatoes. These numbers were comparable to those observed in other L-DOPA accumulating plants. Additionally, the advantage of obtaining L-DOPA from tomatoes was the fact that it did not associate with some of the known drawbacks that hampered plant metabolic production of the drug previously.

The potential benefit of this approach is that L-DOPA extraction from tomatoes could scale up at relatively low cost with the participation of small businesses that could prepare L-DOPA from tomatoes.

Compiled and Edited by Dr. Megha Agrawal & Dr. Shyamasri Biswas.

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ISHA Therapeutics

CONTRIBUTING TO THE SPIRIT OF DRUG DEVELOPMENT

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