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# The Role of Tissue Engineering against COVID-19

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Given that the outbreak of the current coronavirus has been rampant since April 2020, there is a severe need for new diagnostic and treatment strategies to combat infectious diseases around the world. Coronaviruses are single-stranded RNA viruses that have a protein coating that protects them from environmental factors. The main components of this virus are Envelope protein, membrane glycoprotein, spike protein, nucleocapsid protein, and relatively large RNA genome.

The coronavirus infects cells with the help of two proteins: an enzyme called an angiotensin-converting enzyme (ACE2), which helps cells attach, and an enzyme called serine proteinase (TMPRSS2), which causes cell infection. The analysis told that only a small number of human respiratory and intestinal cells have genes that express both ACE2 and TMPRSS2. Among them, three main cell types have been identified:1) Pulmonary cells called "type II pneumocytes" help to maintain air sacs, or alveoli, 2) Intestinal cells called enterocytes, which help the body to absorb nutrients, 3) Globulin cells in the nasal passages that secrete mucus.

Researchers say that recognizing the types of cells that are the main targets of the virus could help future work, including research into future antiviral drugs. The coronavirus attaches to human cells through the ACE2 enzyme and multiplies in the body. Essential goals in tissue engineering (TE) that are being studied include eliminating ACE 2 interactions, changing pH, and inhibiting viral enzymes from preventing proliferation.

Vaccines exist for both respiratory viruses such as Influenza virus and bacteria such as Streptococcus pneumonia and Haemophilus influenza. While the achievement of respiratory viral vaccines varies from season to season, data suggests influenza vaccination generally results in a lower probability of complications, including ICU stay, mechanical ventilation, and severe outcomes, especially in patients with co-morbidities such as chronic obstructive pulmonary disease.

As a modern science, TE is well suited to provide solutions to complex clinical questions. The development of viral in vitro models, drug delivery systems, and vaccine platforms was investigated to fight coronavirus through TE. The ability to vaccinate against particular pathogens has played a significant role in preventative medicine for the last century.

In the last decade, TE caused essential advancements regarding in vitro human cell culture models. Maturation of induced pluripotent stem cells, CRISPR-Cas, microfluidics, 3D printing, and biomaterials have led to technologies such as tissue-on-a-chip and advanced bioreactor models including co-cultures of cells from ectodermal, mesodermal, and endodermal lineages. Using human cells, these models have been able to mimic complex pathophysiology, such as the formation of pulmonary edema upon exposure to inflammatory signs such as interleukin-2.

For instance, in a model to study the influenza a virus, 3D tissue-engineered constructs more accurately recapitulated host morphology of sensitive human epithelial airway cells than 2D culture and infection with dominant influenza strains upregulation of proinflammatory cytokines. One coronavirus-specific case of a tissue-engineered platform in which respiratory viruses have been studied is the rotation wall vessel bioreactor.

These models assume low physiologic shear stress and frequently include various pulmonary cell types, including co-culture of human mesenchymal bronchial, tracheal cells, moreover human bronchial epithelial cells. They are challenging them against respiratory syncytial virus and SARS-CoV-1. The other model, human pulmonary epithelial progenitor cells were developed on a collagen matrix in a serum-free media with a mesenchymal stroma and exposed to a virus. It was proved that stem cells were targeted by SARS-CoV-1, which may suggest why healthy lung regeneration following viral infection is challenging. Several exciting tissue-engineered humans in vitro lung models could be leveraged for studying viral infection and verified in vivo models for respiratory viruses, including non-human primate, already in use. Factors that may improve the relevance of in vitro models include

1. human rather than animal cell lines,
2. co-culture of multiple pulmonary cell lines,
3. 3D scaffolds that mimic the native pulmonary architecture
4. culture methods that permit the generation of the extracellular matrix before viral inoculation.

Further head-to-head studies will need to be performed to determine if these components are necessary to capture the pathophysiology of viral infection. These platforms will be valuable in conducting hypothesis-driven research to understand the host-pathogen interface.

One way to treat the coronavirus is to create a scaffolding system to boost vaccination. By particular physicochemical properties, such as pore size, and profile of released recruitment signals like granulocyte-colony stimulating factor, scaffolds of PLGA, and mesoporous silica rods have been used to recruit and concentrate antigen-presenting cells to vaccine components. This platform of scaffold-based vaccination has also proved its effectiveness against bacterial pathogens in porcine and murine models.

Other cases of scaffold-based vaccine systems include those generated from a respiratory syncytial virus that was effective in mice as well as non-human primates. These particle-based and scaffold-based vaccine systems promising in translation toward SARS-CoV-2; however, the majority have only been studied in mouse models at this point. Significant translational efforts will need to be undertaken for clinical trials. Modular platforms in which different antigens can be plugged in may be beneficial for rapid vaccine development in future pandemics.

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Through the COVID-19 pandemic, one of the essential strains on the healthcare system has been the need for inpatient beds both on ordinary wards and in intensive care units (ICUs). As discussed earlier regarding in vitro drug screens, there are currently limited therapeutics that have clear clinical evidence of improving outcomes such as days of hospitalization required, need for ICU stay, and need for intubation/ventilation. As new small molecule-based therapies come through the pipeline, tissue engineers can continue to design drug delivery systems to: 1) target medications to specific organ systems to increase bioavailability, and 2) extend the release of drugs such that frequent administration is not necessary.

The rate of disease and death from COVID-19 make it unlike than any virus in this century. Scientists are banding together to combat the menace of SAR-CoV-2. Tissue engineers have a rare set of devices. They can make substantial contributions to our understanding of the viral disease and contribute towards the significant development of diagnostic and therapeutic platforms. There is a hope that tissue engineers can create remedies against this current pandemic and work to prevent and mitigate future viral outbreaks in the future. Now, in TISSUEHUB, we are working on creating 3D Scaffolds which mimics the real environment of human lung.