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## Highlights

# The influenza chronicles: From the 1918 pandemic to current understanding of host defense mechanisms

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### ABSTRACT

In this special edition of the *Biomedical Journal*, we learn about the battle between host and influenza virus at the respiratory epithelium, and how the history of influenza pandemics has driven both major advances in the understanding of immunology and planning for future outbreaks. We also learn of a nanoparticle system that holds promise for photodynamic therapy in breast cancer. Finally, we add evidence to the debate of the safety of a minimally invasive technique for aortic valve replacement in elderly patients.

## Spotlight on reviews

### *The influenza chronicles: from the 1918 pandemic to current understanding of host defense mechanisms*

From new emerging strains like the 2009 “Swine” flu, to seasonal, and very often deadly, outbreaks, influenza viruses continue to dominate headlines worldwide. In this special edition of the *Biomedical Journal*, we explore the basic biology of infection, in particular the battlefield taking place at the respiratory epithelium. We catalog the pandemics and epidemics of influenza, where history is unfortunately likely to repeat itself, but from which many valuable lessons have been learned about basic immunology.

Influenza is highly contagious, and the respiratory epithelium is the first site of attack by invading virus particles. In the first review article of this edition, Denny and Ho [1] describe the

intricate and brilliant defense mechanisms launched by the respiratory epithelium and its resident cells populations [Fig. 1] in response to influenza A virus (IAV), the most severe type of influenza and only strain to have caused pandemics. First, the respiratory epithelium presents a complex physical challenge that the intruders must overcome before coming anywhere close to infecting host cells. Epithelial cells are attached to their neighbors through tight junctions and other structures which are linked to the cellular cytoskeleton to form an impermeable mechanical barrier. This barrier is interspersed by cells that secrete an arsenal of defensive proteins and peptides, such as  $\beta$ -defensins, which punch holes in the membrane of invading pathogens [2]. Moreover, epithelial cells are covered in mucus which traps viral particles and brings them into contact with antimicrobial proteins.

The respiratory epithelium however is much more than just a physical barrier. Should IAV penetrate this first line of defense, epithelial cells are able to detect the intruders and

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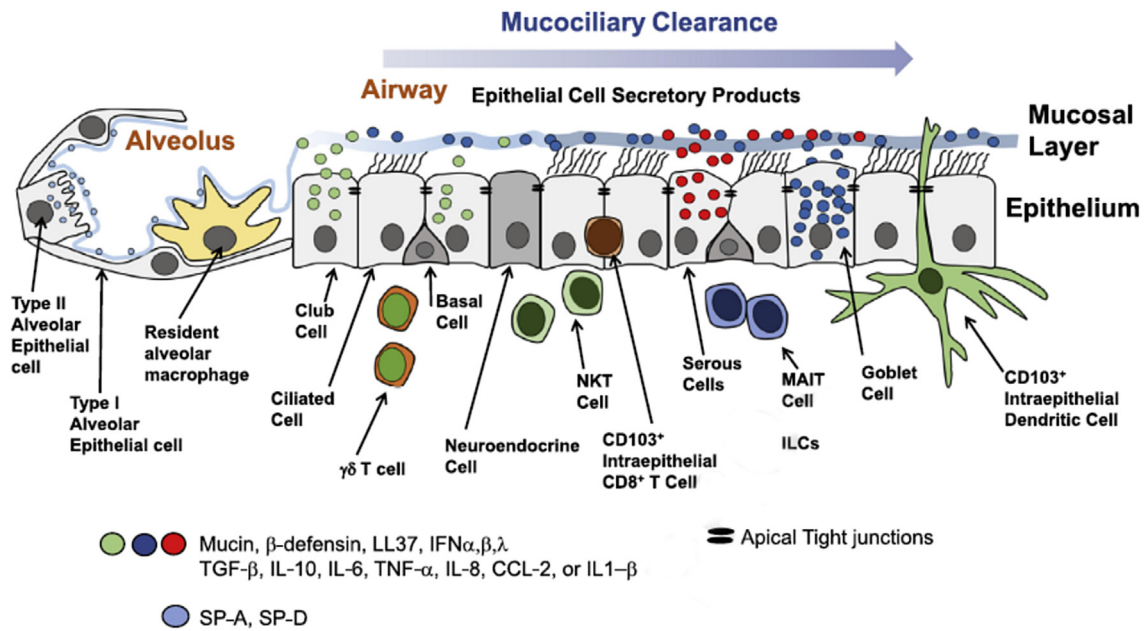


Fig. 1 The respiratory epithelium and its resident immune cell populations. Epithelial cells are densely interconnected through tight junctions and secrete mucins and various other anti-microbial peptides to defend against IAV and other pathogens. Many epithelial cells are ciliated, and sweep evading pathogens upwards via a mucociliary elevator. Several immune cell populations are resident in the respiratory epithelium or closely associated with it. Figure kindly provided by Denny and Ho [1]. See main article for more details.

initiate mechanisms to limit their replication and eliminate them through local and systemic immune responses. Viral particles first enter epithelial cells via endosomes, but soon escape to the cytoplasm and translocate to the nucleus to replicate. Epithelial cells contain a variety of Toll-like receptors (TLR) capable of recognizing IAV at various stages of its journey to the nucleus. A major TLR for the recognition of IAV is the family of RIG-1-like receptors (RLRs). RLRs, like MDA-5 and RIG-1, sense double stranded RNA in the cytoplasm to activate interferon genes [3] and the NLRP3 inflammasome complex [4]. IFN responses in turn limit viral replication. In particular, type I and type III interferons are important for IAV infection. They activate diverse interferon-stimulated genes (ISG), whose main task is to stop the spread of infection. These genes trigger apoptosis, shut down protein synthesis and stimulate innate and adaptive immune responses [5,6]. One ISG, the MxA protein, even interacts with the IAV nucleocapsid directly, halting nuclear import and replication [7]. Viral triggering of the NLRP3 inflammasome on the other hands prompts epithelial cells to release IL-1 $\beta$ , an important, early pro-inflammatory cytokine in IAV and indeed many other infections. Besides stimulating the secretion of other cytokines and chemokines, IL-1 $\beta$  increases the expression of adhesion molecules to recruit neutrophils, monocytes and CD4 T cells to the site of infection [8]. The respiratory epithelium also provides a niche for resident immune cell populations, many of which work to resolve the infection.

The battle at the respiratory epithelium described by Denny and Ho is one unfortunately that has played out constantly over history, as we learn from Gong et al.'s chronicles of influenza outbreaks over the past century [9]. We follow the history of influenza in Taiwan, from the 1918 H1N1 pandemic that caused 25,000 deaths in the country [10], to various other

pandemics and epidemics in living memory. Genetic reassortment leading to the emergence of new strains continues to challenge public health services in the country, and indeed worldwide and has led to the introduction of new vaccines [11] as well as the establishment of an island-wide influenza-monitoring network. Isolated cases of infection with zoonotic strains [12] are also a cause for concern. Despite the devastation brought about by influenza pandemics, in our final review McMichael [13] describes how intense scientific efforts in the wake of the 1918 pandemic shed light on some of the basic principles of T cell immunity. In particular, studies of influenza A virus were instrumental in showing that CD8 T lymphocytes recognize short viral peptides presented by class I molecules of the major histocompatibility complex, and also highlight the role that T lymphocytes play in recovery from infection.

As our knowledge of immunity to influenza viruses increases, so too should our preparedness for handling new outbreaks. Still, with the emergence of new strains and the threat imposed by zoonotic viruses, it may feel like the virus is one step ahead. The development of new technologies for real-time monitoring of genetic changes, and networks for managing new outbreaks will help us to keep pace.

### Spotlight on original articles

#### A “golden” nanoparticle system for photodynamic destruction of breast cancer cells

Photodynamic therapy (PDT) offers a non-invasiveness and less cytotoxic alternative to conventional anti-cancer therapies, but its effectiveness is often hampered by an ability to deliver therapeutic particles to the site of the tumor. In this issue of the

*Biomedical Journal*, Mfouo-Tynga et al. [14] investigate a nanoparticle system that could help to improve PDT for breast cancer.

PDT has proven to be an effective therapy for various cancers over the years [15,16]. This non-invasive treatment works by combining a photosensitizer (PS) with molecular oxygen, which, when combined with light of a specific wavelength, reacts to produce cell-damaging reactive oxygen species (ROS). These ROS in turn attack the tumor cell from within, causing cell death by apoptosis [17]. Similarly, the blood vessels surrounding the tumor may also be destroyed, leading to vascular shutdown [18]. PDT carries fewer side effects than conventional chemo- or radiotherapy: ROS have a short diffusion distance and lifetime, meaning that toxicity is limited to the irradiated area and surrounding normal tissue escapes unscathed.

Despite its advantages, PDT faces a major challenge: effective drug delivery to the site of the tumor. Various nanoparticles (NPs) have been tested to encapsulate the generally hydrophobic PS molecules, ranging from polymeric NPs, liposomes, inorganic/organic hybrid NPs [19]. In this issue, Mfouo-Tynga et al. [14] test whether gold NPs coupled with a PS of sulfonated zinc-phthalocyanine mix could effectively kill breast cancer cells *in vitro*.

In their delivery system, the PS is bound to the surface of the gold encapsulated dendrimer NP. Using a similar NP system, Wieder et al. [20] found that the NP conjugates are effectively taken up by HeLa cells and upon irradiation, are able to kill approximately twice as many cells as achieved by treatment with free phthalocyanine. In line with these findings, Mfouo-Tynga and colleagues report that these gold NP conjugates effectively kill MCF7 breast cancer cells upon irradiation. Cells treated and subsequently irradiated showed distinct changes in morphology and decreased viability, along with an increase in cytochrome c levels, indicative of massive mitochondrial damage that occurs during cell death. This, coupled with the upregulation of the BAX, BCL-2 and CASP-2 genes, confirmed that the cells were dying by apoptosis.

These results show that gold NP conjugates have great potential as delivery vesicles for PDT in the treatment of breast cancer. Moreover, they also reveal conditions under which PDT using the zinc-phthalocyanine mix may be effective, which is no trivial finding because previous experience reveal that the concentration of this PS and wavelength of irradiation must be optimized for each cancer cell line/type [21]. Nonetheless the “punch” of these golden particles still needs to be confirmed *in vivo*.

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## Also in this issue:

### Reviews

#### *Wearable sensors enable “leap forward” for movement disorders*

Jalloul [22] describes how the introduction of increasingly sensitive wearable sensors to monitor movement is allowing a shift from subjective to objective clinical assessment of movement disorders. Such devices have already been used to quantify tremor severity in Parkinson's disease [23], identify elderly individuals at risk of falls [24], and monitor recovery of knee function after surgery [25]. The widespread introduction

of such sensors would greatly facilitate the diagnosis and monitoring of movement disorders but validation of these objectives measures and the development of standards for sensor placement are still needed.

### Original articles

#### *New aortic valve replacement technique found to be safe for elderly patients*

Because of an increase in the incidence of aortic stenosis [26], aortic valve replacement (AVR) surgery is becoming a regular occurrence in operating rooms. Patients are also increasingly presenting with co-morbidities, which puts them at high surgical risk and calls for minimally invasive AVR techniques. Recent advances have enabled the development of a procedure which avoids the placing and tying of sutures, known as sutureless aortic bioprosthesis replacement (SU-AVR); however, this technique remains to be thoroughly investigated in different populations. Here, Lin et al. [27] examine the safety and efficacy of SU-AVR in an elderly Asian patient population. They conclude that SU-AVR is safe for this patient population, leading to excellent valve hemodynamics and an improvement in clinical symptoms, while also offering reduced surgery time and possibility to remove the diseased valve.

#### *Validation of a health literacy tool for Chinese speakers*

Health literacy skills, that is the ability to obtain, understand and use basic health care information, is important for all patients, but in particular those with conditions requiring intensive self-management, like diabetes. The *Newest Vital Sign* is a screening tool that tests reading and numeracy skills to identify patients at risk of low health literacy, originally developed in English and Spanish [28]. Here, Tseng et al. [29] attempt to validate a Chinese version of the tool. In a group of 30 Taiwanese patients with diabetes, Tseng et al. found that the *Newest Vital Sign* performed well against other measures for health literacy, suggesting that this easy and fast tool can be incorporated into diabetes management among the Chinese-speaking population.

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## Conflicts of interest

The author declares no conflicts of interest.

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