Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Microbes and Infection 20 (2018) 451–454

Contents lists available at ScienceDirect

Microbes and Infection

journal homepage: www.elsevier.com/locate/micinf

Editorial

Microbes and Infection turns 20

A B S T R A C T

The journal *Microbes and Infection* is celebrating its vigintennial anniversary and has reunited for this occasion two dozen reviews illustrating achievements of the past as well as future challenges in the field of infectious diseases. From top-notch vaccine development strategies, to high-throughput powered analysis of complex host-pathogen interactions, to innovative therapeutic designs, this issue covers the entire spectrum of pathogens and areas of their confrontation with the host.

1. Introduction

Twenty years ago, *Microbes and Infection* was created.

Twenty years - a decent amount of time measured by the standards of a Human life, a fraction of a wink in History. But in the short history of the field of molecular biology, twenty years are more than enough for major scientific breakthroughs, tragic episodes, large victories, and overthrown dogmas. At the occasion of our twentieth anniversary, we have the honour to present a compilation of a wide variety of reviews, which offer a glimpse at the state of the art in infectious diseases research. And yet - although they depict the present, they also mirror important episodes of the past two decades and foreshadow as well the trials to come.

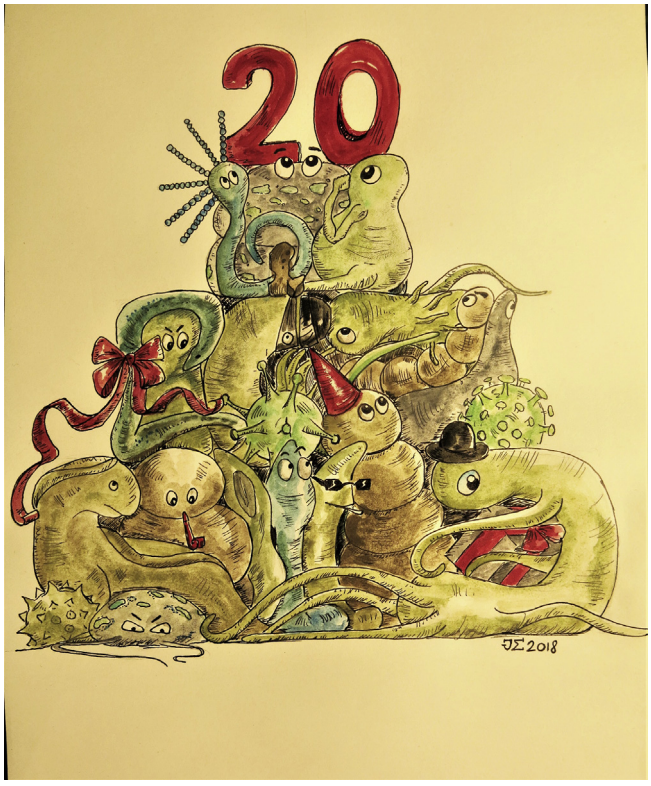

Fig. 1. *Microbes and Infection celebrates* twenty years of publications on host-pathogen interactions.

2. Troubled times

Truly, the last twenty years have been marked by several epidemics, nay the threat of a pandemic. Two highly infectious coronaviruses (SARS and MERS) hit the headlines at about ten years' intervals. At the same time, the media provided ample coverage of seasonal influenza A virus outbreaks, such as H5N1, known as “bird flu” and considered the world's largest current pandemic threat around 2006, the 2009 “swine flu” pandemic caused by H1N1, or the threatening features of H7N9 in 2013. Shortly afterwards, the EBOLA virus (EBOV) went on a rampage in western Africa, killing over 11,000 individuals and annihilating decades of fragile economic progress. More recently, the Zika virus (ZIKV) and its neurological complications reached Latin America in 2017 with a huge epidemic in Brazil.

Despite much scientific progress in our understanding of infectious diseases, the threat emanating from (re-)emerging infectious diseases has increased over the past 2 decades due to the combination of interrelated factors, many of them tainted by human responsibility. Thus far, all candidates for pandemics are zoonoses, and the current meat-heavy agro-alimentary industry contributes significantly to the maintenance of animal reservoirs and an evolutionary playground for many pathogens, while the close contact between animals and humans facilitates the emergence of animal-to-human transmission as well as the drive towards antibiotic resistance. This trend is bound to continue, as food production needs

https://doi.org/10.1016/j.micinf.2018.05.002
1286-4579/

to match the rapidly growing global population, which in turn also favours transmission of microbial pathogens. Furthermore, climate change is constantly broadening the geographic range of a variety of arthropod vectors, and globalization not only shuttles men and merchandise around the planet but also infectious agents. Lastly, let's not forget the pathogens that resist all our attempts at eradication. Despite almost three decades of massive investment into finding a cure and a vaccine for the human immunodeficiency virus (HIV), the latter keeps being one step ahead, principally through phenomenal mutation strategies, nicely summarized in this issue by Nomaguchi et al. [1].

In the eternal arms race between host and microbe, prevention is still better than cure. And when it comes to infectious diseases, prevention equals vaccination. Consistent with this, several of our anniversary reviews advocate for various promising strategies for further vaccine development. They emphasize the advantages of live attenuated vaccines, but also the importance to achieve an equilibrium between adequate attenuation and sufficient residual immunogenicity.

Yun Zhao and colleagues argue convincingly that lipopolysaccharide (LPS) is the ideal knob for fine-tuning live attenuated vaccines for Gram-negative bacteria. The authors carefully review how structural modifications of LPS improve immunogenicity and reduce the virulence of various bacteria [2]. The soundness of the strategy is incidentally exemplified by the review from Pascual et al., who discuss one of the most common, yet often overlooked, zoonotic diseases worldwide - brucellosis, whose agent is an expert in avoiding immune detection through the poor immunogenicity of lipid A, as well as the unusual LPS core structure [3].

With regards to viruses, Frantz et al. propose transforming the Rolls Royce of live attenuated vaccines, the measles vaccine, into a “plug-and-play” platform for the fast development of new potential vaccines, by grafting antigenic proteins from other viruses onto the particularly accommodating measles vaccine [4]. And as for parasites, Low et al. suggest taking advantage of a relatively-unknown organelle: the apicoplast, the exclusive property of Apicomplexan parasites such as *Plasmodium*. This specificity plus the prokaryotic features of the plastid make it an interesting target for drugs. As there is still no efficient vaccine against malaria, the authors recommend that we turn our attention to the plastid. Interestingly, many drugs affecting the apicoplast lead to a “delayed death” phenomenon, where only the second generation of parasites die - theoretically, the ideal conditions for the development for a so-called “suicide vaccine” [5].

3. Times of technology

The development of high throughput sequencing technologies has radically changed the landscape of every field in the life sciences. Microbiology might be the one that managed the greatest thrust into the unknown since the dawn of metagenomics, when thousands and thousands of previously inaccessible life forms could be uncovered in a single sequencing run. Driven by the technological changes, the scientist's viewpoint drastically shifted from the close-up of one element to the wide-angle covering simultaneously the entire system. The frenzy of the need to find the “big picture” led to the conviction that the individual can only be understood in the spatiotemporal context of its surroundings.

An excellent example is provided by Häcker, who relates what happens when the complexity of the pathogen's world pounces on the complexity of the host apoptosis system, leading to the conclusion that there is no such simple thing as “apoptosis in infection” [6]. And even when the complexity of the pathogen world is narrowed down to “only” the influenza A virus (IAV), things stay pretty convoluted, as Downey et al. point out in their review. They emphasize the importance of using *in vivo* models rather than cell cultures because communication between pulmonary macrophages and epithelial cells shape the kinetics of cell death during infection, which are in turn crucial for regulating the antiviral responses [7]. This view is supported by Brizic et al., who describe insights on the neurological damage caused by the human cytomegalovirus (HCMV) gained from a mouse model [8]. But even when down to one receptor, complexity has still the final say. In this research paper in our collection of reviews, the group of Ojcius unravels the versatile role of the mitochondrial NOD-like receptor NLRX1 in the modulation of the NLRP3 inflammasome: it activates the NLRP3 inflammasome upon infection by pathogens but can dampen its effects in the presence of mere commensal pathogens [9].

The “omics”-era also fuelled the rise of the host-pathogen interactome and the study of the microbiome. Bhela and Rouse provide us with a good illustration of the complex host-pathogen interdependence by describing the intricate microRNA (miRNA) network between the herpes simplex virus (HSV) and the human host cell [10]. Other communication forms between host and invader were only discovered recently and remain largely mysterious. Zamith-Miranda et al. gathered the sparse knowledge available about the intriguing fungal extracellular vesicles (EVs), which excel at modulating the host immune system as they please, while integrating stress and environmental signals [11].

Unravelling of the microbiome composition and its influence over nearly every physiological function of the human organism is among the most important and intriguing discoveries of the recent past. Within this framework, Pienkowska and colleagues have assembled here a comprehensive review of the current knowledge concerning the microbial communities of the upper and lower human respiratory tract, including the techniques underlying data generation and analysis, as well as their applications in health and disease [12]. Moreover, Loeper et al. describe how the imbalance of the female urogenital microbiome increases the risk for sexually transmitted infections [13].

However, the notion of individuality did not get lost in the big picture. Quite the contrary - the advent of single cell RNA-sequencing added a new awareness of extreme complexity to the entire system. This aspect is elegantly discussed by Weigel and Dersch. Pathogens live in a constantly changing and mostly hostile environment, where resourcefulness and rapid adaptation are core requirements for survival. Hence, a mixed population is best suited to face sudden challenges. For that matter, another profound dogma change of the past decades has been the rehabilitation of “junk DNA” and “noise” thanks to the discovery of a huge number of long noncoding RNAs and pervasive transcription. Just as the latter is now considered raw material for evolution and adaptation, stochastic fluctuations in gene expression, exacerbated in turn by slight differences in the microenvironment and feedback loops, drive the emergence of subpopulations in a genetically identical population and can be considered a virulence strategy [14].

Countless pathogens evade efficient prevention and treatment mainly because they developed cunning strategies to evade the host immune system, drawing on wits forged by millions of years of co-evolution. The key to defeat them relies on a meticulous observation of these escape and subversion techniques, in the hope to spot a loophole. Major advances in *in vivo* observation techniques have proven crucial to boost the field; thus, a substantial

number of reviews focus naturally on detailing the exchange of blows between host defences and aggressors.

Advanced shape-shifting abilities belong assuredly to the arsenal of many pathogens. With this in mind, Tu and colleagues describe the genetic and molecular events underlying tachyzoite to bradyzoite interconversion of *Toxoplasma gondii*, crucial for establishing a latent infection in tissue cysts [15]; while Löffler and Ebel dedicate themselves to the hardships of the immune system regarding the extraordinary plasticity of many fungi, capable to transit between yeast cells and hyphae and thus very different sizes and surface molecule patterns [16]. Complement-evading strategies in turn can be a serious obstacle for vaccine development. This is the case of *Bordetella pertussis*, the causative agent of whooping cough. Thiriard et al. describe in detail the multiple ways the bacterium can subvert the different steps in complement activation and how this impacts on vaccine efficiency [17].

CovR/S mutants, a hypervirulent update of group A *streptococci* (GAS), target neutrophils, as reported by Langshaw et al. Consequently, the authors underscore the soundness of developing multi-component vaccines, targeting separate virulence mechanisms in parallel [18].

The interplay between pathogens and disease states is a central feature that needs to be considered for the development of realistic treatment strategies. Infectious diseases threaten especially the population of developing countries; thus, factors such as low cost, easy transport and storage, and safe drug administration are crucial. Nyirenda and colleagues draw attention to the fact that the susceptibility to invasive nontyphoidal *Salmonella* infection peaks in young children suffering from malaria and anaemia. Understanding how an already impaired immune system deals with a supplementary aggressor is a major challenge for vaccine development [19].

4. Times of treatments

Treatment strategies have tremendously diversified in conjunction with the continuous discovery of novel host-pathogen interaction networks. The findings have led to previously unimaginable therapies, such as the faecal transplants to treat *Clostridium difficile* infection.

Close observation of the different stages of pathogenesis is pivotal for improved therapy, state Rajasagi and Rouse in their review on herpes stromal keratitits (SK). The authors describe how classical treatment strategies mainly based on anti-viral drugs and corticosteroids could be enriched by lipid pre-resolving mediators, anti-angiogenic agents or manipulation of microRNAs and metabolism [20]. A similar logic underlies the review by Vernel-Pauillac and Werts, who combine the latest insights into how *Leptospira interrogans* escapes the immune system with the most recent tactics for drug and vaccine development. Notably, the authors explain how computational and statistical approaches as well as the CRISPR/Cas9 technology could assist vaccine design [21]. The team of Oliveiro reminds us that sometimes the foe can become a friend, at least in bits and pieces. They make a good case for the use of serine protease inhibitors containing a Kunitz domain normally used by helminth parasites to dampen the host immune system, but which could come in very handy when the latter goes over the top [22]. In turn, Olds et al. plead for the revival of an “ancient universal stress molecule” - abscisic acid (ABA). The versatile stress signalling molecule in plants and animals seems indeed to have many applications: being essential for *T. gondii* growth and development, it might be a therapeutic target; in mammals, the hormone has displayed beneficial properties in a wide range of processes, including glucose metabolism, stem cell proliferation, tumorigenesis, inflammation and depression [23].

Finally, serendipity is sometimes the researcher's best friend. The recent era of epigenetics has popularized the use of drugs influencing the methylation or acetylation state of cells, especially for cancer treatment. The team of Jiang reveals how the new anticancer drug Chidamide, a selective histone deacetylation inhibitor, successfully lures out the HIV-1 provirus from latency - one of HIV's sneakiest features [24].

But enough of the teaser for now - we sincerely wish *Microbes and Infection* a very happy birthday and best wishes to all our readers and contributors on this auspicious occasion.

Conflict of interest

There is no conflict of interest.

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8 May 2018
Available online 30 May 2018