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Highlights

Evergreen influenza – Tackling an old enemy with fresh munitions

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ABSTRACT

This special edition of the *Biomedical Journal* puts the innate immune system into the limelight. We learn about the universal mechanisms underlying the immediate defense against influenza viruses mounted by innate immunity but also its detrimental secondary effects and how differential host genetics influence the network. Moreover, this issue addresses how oral hygiene is a concern for the entire organism, that younger age goes well with neoadjuvant chemotherapy for breast cancer and zinc with feeling less distressed by tinnitus caused by noise-induced hearing loss, and that IL-1Ra holds very promising potential to prevent intestinal ischemia reperfusion injury. Finally, we discover which type of post optimally protects devitalized teeth from breaking and how difficult it is to accurately diagnose the macrofollicular variant of papillary thyroid carcinoma.

Spotlight on reviews

Evergreen influenza – tackling an old enemy with fresh munitions

Time goes by, but influenza remains. One century after the ravages of the worst influenza pandemic ever, the 1918 Spanish Flu, and despite major progress in research and vaccination strategies, influenza persists in being one of the most common viral infections worldwide [1,2]. Moreover, globalization, climate change, the boom of human mobility plus the massive intensification of livestock farming have fanned the embers of pandemic threats over the last decade.

Continuously changing versions of the influenza A virus (IAV) have bestowed on us the H5N1 “bird flu” and the H1N1 “swine flu” pandemics in 2006 and 2009 respectively, as well as the threats by H7N9 in 2013 [3]. On the other hand, the revolution of molecular biology and genetics from the second half of the 20th century on has unveiled bit by bit the sheer complexity of the cellular and molecular mechanisms behind the host pathogen encounter, shaped by the everlasting arms race of co-evolution. This novel understanding of the intricate *ménage à trois* of microbes and both the innate and the adaptive immune system has certainly provided us with a new angle of attack against influenza [4]. However, the fragile balance between efficient pathogen elimination and collateral damage to

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the host has made it extremely difficult to fine-tune the system [5].

The innate immune system in times of influenza - friend and foe
In our first Special Edition review, Carmelo Biondo et al. pay tribute to the complex role performed by the innate immune system upon influenza infection [6]. Until adaptive immunity becomes operational following invasion by the pathogen, it takes a minimum of five days, during which the innate system has to battle and maintain the invader on its own. Unfortunately, it also tends to go too far, leading to excessive systemic inflammation and life-threatening tissue injury [7].

At the cellular level, the authors describe how these defenses are strategically stationed at the organism level, from alveolar macrophages patrolling the boundary to the outside world to dendritic cells presenting viral antigens to naïve lymphocytes. As for the molecular realm, recognition and defense modules are present in all cellular compartments. Biondo et al. walk us in great detail through the sector of Toll-like receptors (TLRs), the interferon system, the plethora of pro-inflammatory cytokines and the inflammasome, always making sure to outline both the protective and potentially detrimental effects of each module [Fig. 1]. In addition, they highlight the crucial role that countless mouse models have played in deciphering the exact role of individual components of the innate immune system, but also their pitfalls. For example, most standard inbred mouse strains lack a functional MX1 and/or MX2 protein and are thus *per se* more susceptible to influenza.

Given the complicated dual role in protection and danger of the majority of the innate immune system, the authors suggest focusing rather on the dampening of downstream effectors, like neutrophil extracellular traps (NETs), production of reactive oxygen species (ROS) or IL-17 secretion.

Nonetheless, after this detailed portrait of the universal interface between innate immunity and influenza infection, Danielle Wellington et al. question this very universality in our second review by addressing how differences in host genetics condition the severity of influenza infection [8]. Despite the era of -omics and the popularity of genome wide association studies (GWAS) for a multitude of features and diseases [9], the matter remains complex because of the strong interdependence with other genetic or environmental factors, lack of clinical samples and the share of viral strain variance [8]. Regardless, a certain number of genetic variations and their links with influenza susceptibility are known to date, all of them from the front lines of host defenses against viral invasion, such as single nucleotide polymorphisms (SNPs) in TLR or antimicrobial genes.

The authors though draw our attention to a more mysterious member of the host pathogen interplay, the interferon induced trans-membrane protein 3 (IFITM3). Mainly induced by interferons of types I and II, IFITM3 inhibits the propagation of many enveloped RNA viruses by preventing the release of viral particles from endosomal compartments, although the mechanistic details are still unclear [10,11].

Intriguingly, IFITM3 presents two SNPs, both associated with an increased severity of influenza infection, but one present mainly in European and the other in Asian

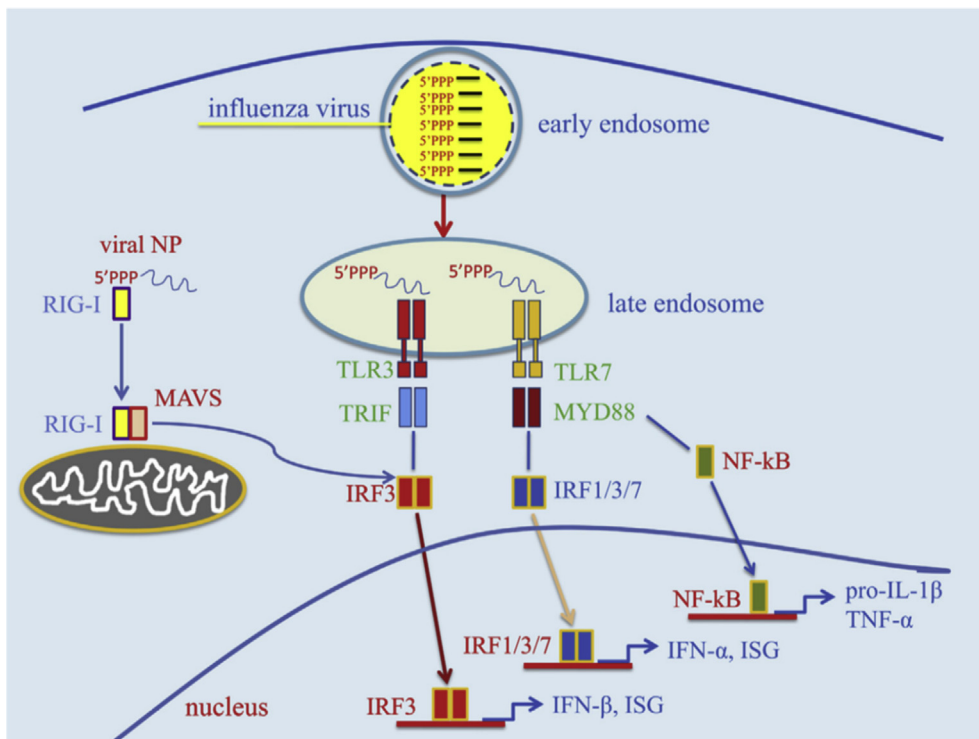


Fig. 1 Example of signal transduction cascades triggered by influenza virus infection. TLR3/7 recognize 5' tri-phosphorylated ssRNA elements and RIG-1 viral RNA, and trigger the NF-κB interferon pathways. Figure kindly provided by Wellington et al. [8]. See main article for details.

populations. The first one, rs34481144, is localized in the gene promoter and seems to prompt epigenetic repression of the entire genomic region by CTCF recruitment, thus lowering IFITM3 expression [12]. SNP rs12252 in turn is to date the most prevalent genetic association with severe influenza infection, yet the underlying mechanisms are unknown so far [13,14]. The authors stress the value that a better understanding of IFITM3 function and tissue-specific expression holds for tuning it eventually to dampen influenza infection severity.

Also in this issue

Reviews

Tooth brushing benefits the entire organism

The oral cavity is home to 500–700 bacterial taxa that compose the oral microbiome, normally living in a mutually beneficial coexistence with the human body [15]. The taking over by pathogenic species leads to gum inflammation known as periodontitis.

Bui et al. focus on an accumulating body of evidence how periodontal pathogens could potentially extend their damage to distant organs and cause systemic disease, either by bacterial dissemination, release of endotoxins and metabolic byproducts into the bloodstream or as a consequence of inflammatory mediators [16]. They present multiple examples strongly suggesting an interrelationship between periodontitis and many diseases including cardiovascular disease, respiratory tract infections, oral and colorectal cancer, diabetes mellitus, Alzheimer's disease and adverse pregnancy outcomes, prompting them to stress the potential of the oral cavity both as a diagnostic tool and target for therapeutic intervention for non-oral systemic diseases.

Original articles

IL-1Ra protects against intestinal ischemia reperfusion injury

Ischemia reperfusion (I/R) injury refers to severe tissue damage caused by secondary inflammation and oxidative stress once the blood supply has been restored. The small intestine is the most sensitive organ to I/R injury, with high fatality rates due to the spread of inflammation to multiple distant organs [22]. The naturally occurring interleukin-1 receptor antagonist (IL-1Ra) has already attracted quite some interest as for its potential ability to counteract IL-1 in inflammation and autoimmune diseases [23,24]. Here, Jin et al. explore its effect on intestinal I/R injury in a rat model [25]. They demonstrate that IL-1Ra administration substantially reduces tissue damage, apoptosis, inflammation and oxidative stress. Besides the expected inhibition of IL-1 targets, the authors provide evidence for an activation of the Nrf2/HO-1 pathway by IL-1Ra as a molecular mechanism underlying the dampening of reactive oxygen species. The results could indicate a novel, promising therapeutic application of IL-1Ra in intestinal I/R injury patients.

Zinc supplementation improves the perception of disease severity in patients with noise-induced hearing loss

High zinc concentrations in the cochlea, ensuring the activity of the superoxide dismutase SOD1, protect the sensitive hair

cells from damage by reactive oxygen species [20]. Tinnitus is one of the most frequent hearing disturbances and due to the spontaneous depolarization of auditory fibers, creating noise without any acoustic stimulus, but its pathophysiology is still unclear. Several studies have observed hypo-zincemia in tinnitus patients and some an improvement of the condition after zinc supplementation, while others report no effect. These discrepancies might be linked to the heterogeneity of tinnitus patients. Therefore, Yeh et al. investigate here the effectiveness of zinc supplementation in a subgroup of noise-induced hearing loss patients suffering additionally from tinnitus [21]. They conclude that although there were no improvements in objective hearing parameters, 85% of patients showed amelioration in a subjective evaluation of life quality restriction due to the tinnitus.

Optimization of post systems for tooth restoration after root canal treatment

Root canal treatment consists in the removal of the nerve of the tooth, which often entails a substantial structure loss that renders the tooth highly weakened. Functional restoration usually requires a post to support a core by increasing the surface between tooth and reconstruction. The rigidity and stiffness of the post material influences its resistance to the permanent mechanical stresses exerted on teeth. Öztürk et al. undertake a comparison of the fracture resistance and mode of extracted and endodontically treated thin-walled teeth restored with different post systems by subjecting them to increasing mechanical constraints [26]. The authors find that the cast post displays the highest and the I-TFC post the lowest fracture resistance, while a glass-fiber post and an I-TFC post allow for tooth repair following fracture.

The challenging diagnosis of macrofollicular variant of papillary thyroid carcinoma

The macrofollicular variant of papillary thyroid cancer (MFVPTC) is a rare subtype of the follicular variant of papillary thyroid carcinoma (FVPTC) [27]. Although the clinical course tends to be indolent, delayed recurrence and extensive lymph, bone or lung metastases can occur in some cases, stressing the importance of correct diagnosis. Even so, the latter is complicated by the similarities with benign lesions [28]. In order to refine diagnostic reference points, Ng et al. retrospectively skimmed the thyroid cancer database for specific MFVPTC features [29]. According to their study, generic diagnosis tools such as ultrasonography (US) and fine needle aspiration cytology (FNAC) are suboptimal for MFVPTC recognition because the consensus malignant US features are not always present in these tumors and the nuclear features too subtle to be observed by FNAC. Given that the 100% survival rate after MFVPTC surgery, an improved diagnosis seems advisable.

Younger age correlates with better outcomes after neoadjuvant chemotherapy in locally advanced breast cancer

Neoadjuvant chemotherapy (NAC) is routinely used in order to reduce the tumor size prior to surgery of advanced breast cancer [17]. The absence of residual invasive tumor in the tissue sample removed during surgery is termed pathological complete response (pCR) and has been shown to predict

favorable long-term outcomes. Various parameters have been correlated with higher pCR rates. Yet, the influence of age on either pCR or locoregional recurrence (LRR) after NAC have not been extensively assessed, although one study finds that younger age is a predictor for LRR after breast-conserving surgery (BCS) but not mastectomy [18]. Here, Chou et al. investigate the connection between patient age and either pCR or LRR after NAC. In contrast to the previous study, the authors find that younger age is an independent factor to predict both pCR and LRR-free survival [19].

Conflicts of interest

The author declares no conflict of interests.

REFERENCES

- [1] Nickol ME, Kindrachuk J. A year of terror and a century of reflection: perspectives on the great influenza pandemic of 1918–1919. *BMC Infect Dis* 2019;19:117.
- [2] Krammer F, Smith GJD, Fouchier RAM, Peiris M, Kedzierska K, Doherty PC, et al. Influenza. *Nat Rev Dis Primers* 2018;4:3.
- [3] Häfner SJ, Ojcius DM. Microbes and infection turns 20. *Microb Infect* 2018;20:451–4.
- [4] Gordon S. Legacy of the influenza pandemic 1918: Introduction. *Biomed J* 2019;42:5–7.
- [5] Pulendran B, Maddur MS. Innate immune sensing and response to influenza. *Curr Top Microbiol Immunol* 2015;386:23–71.
- [6] Biondo C, Lentini G, Beninati C, Teti G. The dual role of innate immunity during influenza. *Biomed J* 2019;42:8–18.
- [7] Cole SL, Ho LP. Contribution of innate immune cells to pathogenesis of severe influenza virus infection. *Clin Sci* 2017;131:269–83.
- [8] Wellington D, Laurenson-Schafer H, Abdel-Haq A, Dong T. IFITM3: how genetics influence influenza infection demographically. *Biomed J* 2019;42:19–26.
- [9] Kenney AD, Dowdle JA, Bozzacco L, McMichael TM, St Gelais C, Panfil AR, et al. Human genetic determinants of viral diseases. *Annu Rev Genet* 2017;51:241–63.
- [10] Brass AL, Huang IC, Benita Y, John SP, Krishnan MN, Feeley EM, et al. The IFITM proteins mediate cellular resistance to influenza A H1N1 virus, west nile virus, and dengue virus. *Cell* 2009;139:1243–54.
- [11] Feeley EM, Sims JS, John SP, Chin CR, Pertel T, Chen L-M, et al. IFITM3 inhibits influenza A virus infection by preventing cytosolic entry. *PLoS Pathog* 2011;7:e1002337.
- [12] Allen EK, Randolph AG, Bhangale T, Dogra P, Ohlson M, Oshansky CM, et al. SNP-mediated disruption of CTCF binding at the IFITM3 promoter is associated with risk of severe influenza in humans. *Nat Med* 2017;23:975–83.
- [13] Zhang YH, Zhao Y, Li N, Peng YC, Giannoulitou E, Jin R-H, et al. Interferon-induced transmembrane protein-3 genetic variant rs12252-C is associated with severe influenza in Chinese individuals. *Nat Commun* 2013;4:1418.
- [14] Prabhu SS, Chakraborty TT, Kumar N, Banerjee I. Association between IFITM3 rs12252 polymorphism and influenza susceptibility and severity: a meta-analysis. *Gene* 2018;674:70–9.
- [15] Krishnan K, Chen T, Paster BJ. A practical guide to the oral microbiome and its relation to health and disease. *Oral Dis* 2017;23:276–86.
- [16] Bui FQ, Almeida-da-Silva CLC, Huynh B, Trinh A, Liu J, Woodward J, et al. Association between periodontal pathogens and systemic disease. *Biomed J* 2019;42:27–35.
- [17] Derks MGM, van de Velde CJH. Neoadjuvant chemotherapy in breast cancer: more than just downsizing. *Lancet Oncol* 2018;19:2–3.
- [18] Mamounas EP, Anderson SJ, Bear HD, Julian TB, Geyer Jr CE, Taghian A, et al. Predictors of locoregional recurrence after neoadjuvant chemotherapy: results from combined analysis of national surgical adjuvant Breast and Bowel Project B-18 and B-27. *J Clin Oncol* 2012;30:3960–6.
- [19] Chou HH, Kuo WL, Yu CC, Tsai HP, Shen SC, Chu CH, et al. Impact of age on pathological complete response and locoregional recurrence in locally advanced breast cancer after neoadjuvant chemotherapy. *Biomed J* 2019;42:66–74.
- [20] McFadden SL, Ding D, Reaume AG, Flood DG, Salvi RJ. Age-related cochlear hair cell loss is enhanced in mice lacking copper/zinc superoxide dismutase. *Neurobiol Aging* 1999;20:1–8.
- [21] Yeh CW, Tseng LH, Yang CH, Hwang CF. Effects of oral zinc supplementation on patients with noise-induced hearing loss associated tinnitus: a clinical trial. *Biomed J* 2019;42:46–52.
- [22] Nadatani Y, Watanabe T, Shimada S, Otani K, Tanigawa T, Fujiwara Y. Microbiome and intestinal ischemia/reperfusion injury. *J Clin Biochem Nutr* 2018;63:26–32.
- [23] Perrier S, Darakhshan F, Hajduch E. IL-1 receptor antagonist in metabolic diseases: Dr Jekyll or Mr Hyde? *FEBS Lett* 2006;580:6289–94.
- [24] Arend WP. The balance between IL-1 and IL-1Ra in disease. *Cytokine Growth Factor Rev* 2002;13:323–40.
- [25] Jin C, Fu WL, Zhang DD, Xing WW, Xia WR, Wei Z, et al. The protective role of IL-1Ra on intestinal ischemia reperfusion injury by anti-oxidative stress via Nrf2/HO-1 pathway in rat. *Biomed J* 2019;42:36–45.
- [26] Öztürk C, Polat S, Tunçdemir M, Gönüldaş F, Şeker E. Evaluation of the fracture resistance of root filled thin walled teeth restored with different post systems. *Biomed J* 2019;42:53–8.
- [27] Albores-Saavedra J, Gould E, Vardaman C, Vuitch F. The macrofollicular variant of papillary thyroid carcinoma: a study of 17 cases. *Hum Pathol* 1991;22:1195–205.
- [28] Yeo M-K, Bae JS, Oh WJ, Park GS, Jung CK. Macrofollicular variant of papillary thyroid carcinoma with extensive lymph node metastases. *Endocr Pathol* 2014;25:265–72.
- [29] Ng SC, Huang BY, Kuo SF, Hsueh C, Chiang KC, Chen CH, et al. Diagnostic pitfalls and therapeutic outcomes of the macrofollicular variant of papillary thyroid carcinoma. *Biomed J* 2019;42:59–65.