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.

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Highlight

SARS attacks!☆

If someone could claim the dubious title of the first major emerging pathology of the 21st century, it is without doubt the severe acute respiratory syndrome (SARS). On November 16th 2002, the first case of an atypical serious pneumonia lacking an identified infectious agent was reported in the Guangdong province of China and spread soon after from Hong Kong, Vietnam and Canada around the planet. What we retain from this episode that skirted the pandemia are its prominent media coverage (panic sells), a slight hitch in international communication as the Chinese authorities took some time to inform the World Health Organization (WHO) and the efficient cooperation leading to the fast identification and sequencing of the *corpus delicti* – a novel coronavirus termed SARS-CoV – by laboratories from the U.S.A, Canada, Hong Kong, Germany, France and China by the end of March 2003 [2]. In comparison, identification of Human Immunodeficiency Virus (HIV) took about two years. During the following decade, research focused on the usual suspects, that are proteins, in infection, virulence and antibody development. Yan Li et al. played the originality card by identifying GU-rich pieces of the SARS-CoV genome as the David defying the Goliath of the host immune system [1].

Coming across extracellular DNA and RNA swimming around when you are a cell is usually bad news, as they stem either from agonizing companions or from nasty intruders, all the more when you happen to be a member of the innate immune system equipped with some pattern recognition receptors (PRRs). Among them, Toll-like receptors TLR3 and TLR9 have been proven to recognize double-stranded RNA and unmethylated CpG-rich bacterial or viral DNA respectively a while ago [3,4]. The fact that ssRNA also activates the immune system is more recent news though. Florian Heil and colleagues provided the first concrete evidence in 2004 by feeding the GU-rich single-strand RNA40 (ssRNA40) from HIV-1 to human and murine macrophages and dendritic cells [5]. The resulting bottom line is that murine TLR7 and human TLR8 recognize single-strand GU-rich RNA and trigger the secretion of inflammatory and regulatory cytokines. Moreover, immune cells are not the only cell population at risk, as TLR7 is expressed in a wide range of different types of neurons as well as in astrocytes and microglia. Lehmann et al. demonstrated that ssRNA40 causes neuronal cell death in mice through binding to TLR7 activating subsequently MyD88 and caspase-3 in a cell-autonomous manner exacerbated by microglial inflammatory ssRNA40/TLR7 dependent signaling, while TLR7−/− mice are entirely protected against ssRNA40 induced neuronal death [6].

Nevertheless, only a few concrete examples of viral ssRNA have been identified and experimentally validated as TLR7/8 agonists until now, among them ssRNA40 and the SARS-CoV culprits described by Li et al. Thus, an interesting question is how widespread the feature of owning GU-rich ssRNAs to drive immune cells crazy is. Obviously it is not restricted to a specific viral genus: HIV-1 is a lentivrus, SARS-CoV a coronavirus and a certain flavivirus, the Langat virus (LGTV), looks like another good candidate based on data in press provided by Baker et al. linking TLR7 to the regulation of the neuroinflammatory response to LGTV infection in the CNS [7]. However, the newcomer and outsider among its own genus SARS-CoV, whose overall level of similarity with other coronaviruses is reduced, might have put the finishing touches to this useful tool made of ssRNAs.

By the way, where doTLR7/8 encounter their viral ssRNA ligands? Given that both receptors are localized in the endosome, it is rather likely that ssRNA ends up there after receptor-mediated endocytosis of the virus or fusion of the viral particle and the infected cell. The strict compartmentalization is a must, as ssRNA with GU-motives is not an exclusive brand of the viral genome and several autoimmune diseases like systemic lupus erythematosus (SLE) or reumathoid arthritis correlate with CpG DNAs and RNA in extracellular compartments as well as the production of autoantibodies against endogenous RNA [5,7]. Host-released extracellular RNA is also frequently detected in brains of neurodegenerative disorder patients like Alzheimer's disease, where it contributes in spreading damage of the central nervous system (CNS) through TLR signaling [6].

Preventing the immune system from going berserk with lethal side-effects at the sight of released nucleic acids turns out to be a tricky one due to the redundancy of the TLR family (10 members in humans). Lee and colleagues proposed

☆ Article highlight of "Extraordinary GU-rich single-strand RNA identified from SARS coronavirus contributes an excessive innate immune response" by Yan Li et al. [1].

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recently a strategy relying on nucleic acid-binding cationic polymers as anti-inflammatory agents [8]. Indeed, hexadimethrine bromide (HDMBr) and 1,4-diaminobutane core-PAMAM-G3 (PAMAM-G3) are able to counter the immune stimulatory effect of all nucleic-acid TLR ligands in multiple inflammatory cell types *in vitro* and *in vivo*, acting as molecular scavengers both neutralizing the free nucleic acids and altering their intracellular distribution.

Therefore, among the potential therapeutical implications of the findings of Li and colleagues figure the occasion to use viral ssRNA as adjuvants for vaccination and immunotherapy [5] as well as the possibility to stop the escalating immune response by blocking the activation of TLR7/8 by ssRNA either from bacterial or viral attack or inappropriate autoimmune TLR activation [7].

After all, the second merit of SARS will be to have boosted the career of antiviral drug research against coronaviruses, as good as inexistent before 2003.

Also, better keep away from civets.

Biosketch

Yan Li obtained the title of Doctor of Medicine in 1998 and his PhD in 2001 both at the Third Military Medical University of Chongqing in China. After three years as a postdoctoral fellow at the Beijing Genomics Institute of the Chinese Academy of Sciences and a year as a visiting researcher at the Faculty of Life Science at the Copenhagen University, he became in 2005 an associate professor and in 2008 the vice director of the Medical Research Center of the Southwest Hospital at the Third Military Medical University of Chongqing.

Interview with Yan Li

What triggered your interest in SARS and ssRNA?

My background comprises microbes, immunology, genomics and bioinformatics. I took part in the work of SARS genome sequencing in the Beijing Genomics Institute et the Chinese Academy of Sciences in 2003 [9]. Now I am majoring in the study on the PAMP and TLRs. Given this, I am in general interested in the topic.

What was your first reaction when you faced the results? Did you expect them?

No, this discovery was somewhat occasional. The first reaction was to consider it quite interesting.

How will the project go on?

We will look for antagonists of TLR7 and TLR8.

What is the take-home message of the article?

An important pathogen-associate molecule was newly discovered in SARS-CoV.

Do you have a personal motto, quote or leading sentence?

More reading, more thinking, more investigation, do not let a clue off.

What advice would you give to the young next-generation scientists?

Work hard, play hard.

What is your favorite hang-out method after a tough day at the lab?

I like fishing.

In your opinion, what are the three most important (scientific) discoveries of the last decade?

Cancer pathogenesis, gene regulation associated with life and appearance based on system biology and the new generation of anti-virus medicine.

If you could travel back in time – what historical personality would you like to meet and what scientific discovery to assist to?

I prefer focusing on something over somebody, thus I would like to widely read the literature in order to resolve current questions.

If you could travel forth in time – what eventual invention would you like to check out?

Maybe Chinese chopsticks. Scientific exploration is endless.

Background

- Severe Acute Respiratory Syndrome (SARS) of unknown etiology appeared in late 2002 in China and spread over 25 countries around the world in barely five months.
- Infection is characterized by fewer followed by a dry cough and shortness of breath. Respiratory failure leads to death in 3–10% of cases.
- March 2003, the causative agent was identified as a novel coronavirus named SARS-CoV having no close relationship with previously characterized coronaviruses transmitted to human by the palm civet.
- Coronaviruses are positive-strand enveloped viruses who represent major pathogens in mammals and birds, causing enteric and respiratory diseases.

In A Nutshell

- The SARS-CoV genome displays a high distribution of GU-rich fragments.
- SARS-CoV GU-rich single-strand RNAs are recognized by host toll-like receptors TLR7 and TLR8 leading to high production of pro-inflammatory cytokines TNF-a, IL-6 and IL-12.
- Injection with SARS-CoV ssRNAs induces an overactive inflammatory response, lung injury and high mortality in mice.

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