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Neo-virology: The raison d’etre of viruses

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ABSTRACT

Given that approximately 10^{31} virus particles exist on Earth and all of them are parasitic in living organisms, it is not hard to imagine how virus infection might affect the physiology of hosts and their ecosystems. However, traditional virology research tends to focus on viral pathogenicity or the individual pathogenic viruses; hence, the significance of viruses and viral-mediated processes in the global ecosystem has been poorly understood. To identify the previously unrecognized “raison d'etre of viruses” in nature, we established a research community, designated as the ‘Neo-virology’ consortium. In this consortium, we define a virus as a component of the global ecosystem and our aim is to elucidate its key roles in host organisms, that is, the intra-host ecosystem.

1. Research goals

An ecosystem is a complex network of interactions involving living organisms and the nonliving components of the environment. Generally, any cellular life form is defined as belonging to one of three domains: the archaea, bacteria, or eukaryote domain, and therefore, viruses are not currently considered to be living components of the global ecosystem. However, given that approximately 10^{31} virus particles exist on Earth (Hamilton, 2006; Suttle, 2007) and all of them are parasites of living organisms, virus infections are likely to affect the physiology of hosts and consequently their ecosystem.

In traditional virology, we have focused on pathogenic viruses that are harmful to their hosts, and have worked to reveal the mechanisms of viral replication and pathogenicity in an effort to conquer viral diseases since the discovery of tobacco mosaic virus at the end of the 19th century. However, the relationships between viruses and hosts are extremely diverse. In fact, recent studies have suggested that viral infections can sometimes be beneficial to the biological functions and/or evolution of the host. To reveal the “raison d'etre” of viruses in nature, we recently organized a joint research group, designated as the ‘Neo-virology’ consortium, which is supported by Grants-in-Aid for Scientific Research on Innovative Areas from the Ministry of Education, Culture, Science, Sports, and Technology (MEXT) of Japan (Table 1). In this consortium, while defining viruses as components of the global ecosystem, we aim to elucidate the ecological and physiological roles of viruses as non-pathogens in host organisms and the global ecosystem. Our project consists of three research units: A01 ‘Coevolution’, A02 ‘Symbiosis’, and A03 ‘Diversity’ (Fig. 1).

2. A01: coevolution

Retroviruses are found in almost all mammals and other vertebrates, and approximately 8% of the human genome is composed of retroviruses in the form of endogenous proviruses (Jern and Coffin, 2008). Some endogenous retroviruses have been shown to play beneficial roles in their hosts, including in the formation of the placenta (Mi et al., 2000; Aswad and Katzourakis, 2012) and the protection of host cells from infection with exogenous retroviruses in some mammals (Aswad and Katzourakis, 2012; Stoye, 2012; Mura et al., 2004). Recent studies have shown that nonretroviral RNA viruses are also endogenized in many mammalian species. For example, Tomonaga’s group discovered that Bornaviruses, a family of non-segmented, negative-strand RNA viruses, have been endogenized in the genomes of many mammals including humans (Horie et al., 2010), and showed potential roles for endogenous nonretroviral elements in antiviral defense (Fujino et al., 2014) and in transcriptional gene regulation (Sofuku et al., 2015). Since a large number of endogenous viral elements have accumulated in host genomes, understanding their importance to the biological function and evolution of hosts is considered to be essential. Hence, in the A01 "Coevolution" unit, we will conduct comprehensive screens to identify endogenous virus-like elements in various eukaryotic hosts. In addition to a deep sequencing approach, we will generate a sequence retrieval

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Table 1
Organization of the Neo-virology consortium.

	Project leader	Institution	
	Yoshihiro Kawaoka	The institute of Medical Science, the University of Tokyo	
Units	Principal investigators	Institutions	Research topics/keywords
A01: Coevolution	Keizo Tomonaga	Institute for Frontier Life and Medical Sciences, Kyoto University	● Mammalian endogenous RNA viruses ● Infection memory ● Coevolution of hosts and viruses
	Hirofumi Sawa	Research Center for Zoonosis Control, Hokkaido University	● Endogenous virus and virus element ● Microbiome networks in arthropods ● Coevolution of hosts and viruses
	Yoshiharu Matsuura	Research Institute for microbial Diseases, Osaka University	● Evolution of Flaviviruses ● Symbiosis of pegiviruses ● Coevolution of hosts and viruses
A02: Symbiosis	Yasushi Kawaguchi	The institute of Medical Science, the University of Tokyo	● Herpesvirus ● Homeostatic mechanisms ● Symbioses with viruses
	Tokiko Watanabe	The institute of Medical Science, the University of Tokyo	● Influenza virus ● Symbiotic relationships between viruses and hosts ● Novel viruses in wildlife
A03: Diversity	Nobuhiro Suzuki	The institute of Plant Science and Resources, Okayama University	● Yadonushi/yadokari viruses ● Symbiotic relationships between viruses and hosts ● Novel virus lifestyles in wildlife
	Hideki Takahashi	Graduate School of Agricultural Science, Tohoku University	● Plant viruses ● Control of environmental stresses ● Virus diversity
	Keizo Nagasaki	Faculty of Agriculture and Marine Science, Kochi University	● Aquatic viruses ● Host-virus coexistence in dynamic equilibrium ● Virus diversity

program to detect virus-like elements, which do not have any sequence homology to current viruses, in mammalian genomes. We will elucidate the effects of the identified endogenous virus-like elements on the biological functions and/or evolution of their hosts. Understanding the coevolution of viruses and hosts is the goal of this research unit.

3. A02: symbiosis

Some viruses have symbiotic relationships with their hosts without causing diseases. For example, latent infection with murine herpesviruses induces systemic activation of macrophages, which then protect the mice from subsequent bacterial infections with either *Listeria*

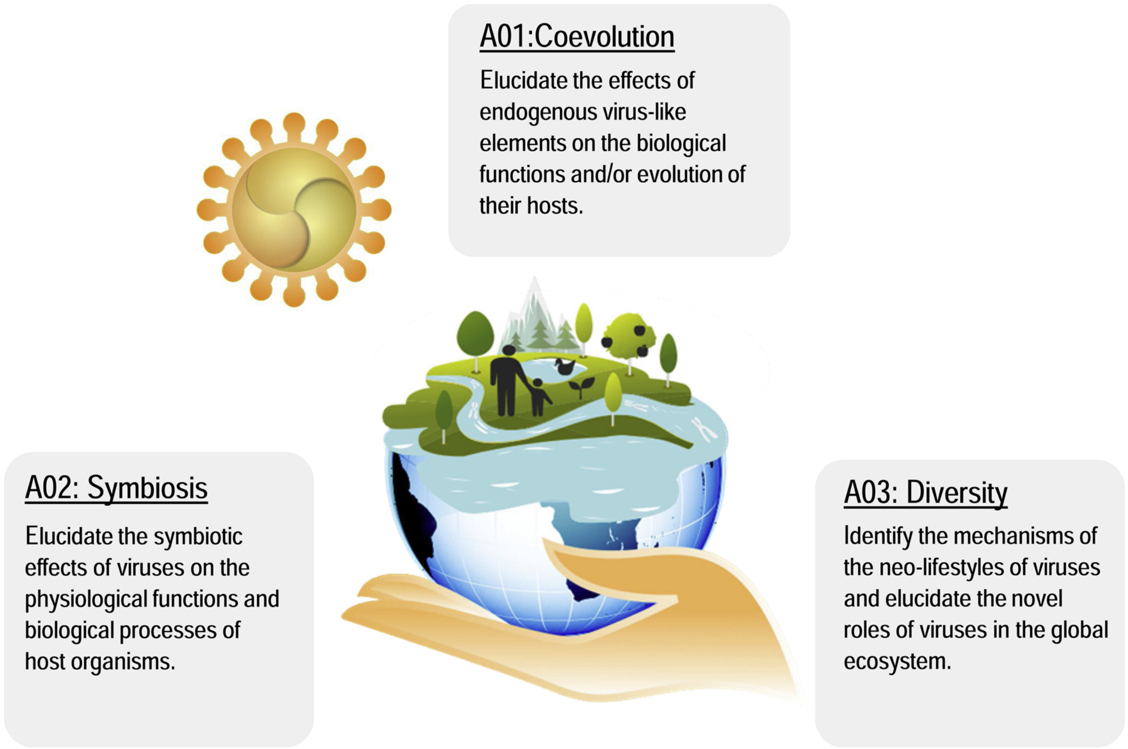

Fig. 1. Scheme of the Neo-virology consortium.
The Neo-virology consortium consists of three research units: A01 'Coevolution', A02 'Symbiosis', and A03 'Diversity'. In this consortium, we define a virus as a component of the global ecosystem and our aim is to elucidate its roles in host organisms (i.e., the intra-host ecosystem).

monocytogenes or *Yersinia pestis* (Barton et al., 2007). Moreover, the infection of non-obese diabetic mice with a lymphotropic virus was shown to prevent the infected mice from becoming type I diabetics (Oldstone, 1988), and the chronic viral infection of mice with murine cytomegalovirus was shown to increase epithelial turnover and wound repair via antiviral cytokine type I interferons (Sun et al., 2015). Therefore, in the A02″Symbiosis" unit, we will elucidate the symbiotic effects of viruses on the physiological functions and immune responses of hosts, and determine the functional mechanisms involved, which will lead to a better understanding of the essential roles of viruses in the regulatory biological processes of host organisms.

4. A03: diversity

Since the first discovery of a vertebrate virus at the end of 19th century, new virus species that infect humans have been identified almost every year. Currently, there are approximately 263 viruses from 25 viral families that are known to be able to infect humans according to the latest International Committee on Taxonomy of Viruses (ICTV) report (Carroll et al., 2018). Global viral surveillance projects, such as the Emerging Pandemic Threats PREDICT program (https://ohi.vetmed.ucdavis.edu/programs-projects/predict-project) and the Global Virome Project (http://www.globalviromeproject.org), have been conducted. The Global Virome Project estimates that ~1.67 million yet-to-be-discovered viral species from key zoonotic viral families exist in mammalian and avian hosts, and project participants predict that 631,000–827,000 of these unknown viruses have zoonotic potential (Carroll et al., 2018).

In addition to viral surveillance in mammalian and avian hosts, Zhang and Holmes's group recently conducted a screen for RNA viruses in diverse host species (more than 186 species other than mammals and birds) and identified about 200 vertebrate-associated RNA viruses in fishes, reptiles, and amphibians (Shi et al., 2018). The recent progress in next-generation sequencing (NGS) technologies and data analyses have enabled the discovery of a wide variety of new viruses (Koonin and Dolja, 2018), many of which do not cause diseases in their hosts. Indeed, recent viral metagenomic studies using NGS technologies and bioinformatic analyses identified a large number of viruses in environmental samples, including plants and oceans (Roossinck, 2015; Gregory et al., 2019). Also of note is that recent virus hunting has led to the revelation of novel virus lifestyles in filamentous fungi (Zhang et al., 2016; Kanhayuwa et al., 2015). In the A03″Diversity" unit, we propose to conduct comprehensive screens to identify viruses that are yet-to-be discovered, in particular, in protoctista and prokaryotes. We will also identify the mechanisms of the as-yet-unexplored neo-lifestyles and neo-lifecycles of these newly identified viruses, which will lead us to understand the novel roles of these viruses in the global ecosystem.

The Neo-virology project is expected to lead to the establishment of a new research field to understand the roles of viruses in living organisms and in the global ecosystem. It has the potential to generate new uses for viruses as tools to regulate ecosystems, and may solve serious environmental problems, such as global warming, CO_2-induced climate change, and desertification. In the near future, we anticipate that this research project will develop into an important scientific field that examines the interactions between the global ecosystem and viruses.

Other remarks

The "Neo-virology" project is being supported by MEXT as one of the Grants-in-Aid for Scientific Research on Innovative Areas, and is expected to develop new virus concepts. "Neo-virology" has sponsored symposia and workshops where scientists from all over the world could discuss neo-virology (e.g., http://www.c-linkage.co.jp/jsv66/en/program.html; http://awaji-forum.com/en/2018/program). The project has been well received by both the scientific community and the general public.

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