【Grant-in-Aid for Scientific Research (S)】

Biological Sciences (Medicine, Dentistry, and Pharmacy)

Title of Project : Identification of higher-order-epigenetic modification machineries and development of potential novel therapeutics in severe virus infection

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Research Project Number : 17H06179 Researcher Number : 50231163
Research Area : Critical Care Medicine
Keyword : Virus, Epigenetics

【Purpose and Background of the Research】

Influenza viruses are a major cause of morbidity and mortality especially among humans with high risk factors, such as diabetes and cancers. Also, highly pathogenic strains (e.g. A/H5N1 virus) show high mortality rates up to 60% in humans. Patients with severe influenza show acute respiratory distress syndrome (ARDS), which requires critical cares in the ICU. To date, the therapies in patients with severe influenza are limited, with currently available anti-influenza drugs that primarily target viral proteins, showing disappointing results most likely due to the emergence of mutated viruses. Influenza virus is a RNA virus, and transcription and replication of the virus genome occur in the nucleus. It is important to find the strategies targeting rather host nuclear system less permissive to viral replication.

Recent high-resolution chromatin interaction maps using chromosome conformation capture (3C) techniques have defined units of chromatin, termed topologically associated domains (TADs). In addition, the insulator protein CCCTC-binding factor (CTCF) is known to act as borders of TADs and play a role in the formation and maintenance of long-range chromatin loops. However, it remains unknown the changes in host chromatin architectures and histone modifications to different pathogenisity of viruses. Nor is it known how such higher-order host epigenetic response can influence the pathogenesis of influenza virus infection.

【Research Methods】

Using different strains of influenza viruses (e.g. H1N1 and H5N1), 1) we plan to analyze the dynamic changes in higher-order epigenetic responses in the host cells to virus infection, which include histone modifications (ChIP-seq), higher-order chromatin structures (3C-based 4C-seq and Hi-C). The host nuclear proteins interacted with virus proteins (mass-spectrometry), as well as the chromatin domains associated with virus proteins (ChIP-seq) will be analyzed; 2) how such higher-order host epigenetic responses affect the pathogenesis of influenza virus infection using host genome-edited cell and mice, and genetically modified viruses; 3) based on the data from 1) and 2), we plan to establish the prediction system to identify the high risk factors for severe influenza and explore the potential for early diagnosis and preemptive cares; 4) the candidate compounds targeting higher-order epigenetic modifications will be screened and we plan to explore the potential for novel drug development. .

【Expected Research Achievements and Scientific Significance】

This project, for the first time can identify the changes in host higher-order epigenetic responses to different strains of influenza viruses. In addition, the possible mechanisms by which such epigenetic changes can influence the pathogenesis of severe influenza will be clarified. Those data could be important information to develop novel therapeutics for severe virus infections.

【Publications Relevant to the Project】

1. Morita M, Kuba K, Ichikawa A, Nakayama M, Katahira J, Iwamoto R, Watanebe T, Sakabe S, Daidoji T, Nakamura S, Kadowaki A, Ohto T, Nakanishi H, Taguchi R, Nakaya T, Murakami M, Yoneda Y, Arai H, Kawaoka Y, Penninger JM, Arita M, Imai Y. The lipid mediator protectin D1 inhibits influenza virus replication and improves severe influenza. Cell. 2013 28;153(1):112-25.
2. Haarhuis JHI, van der Weide RH, Blomen VA, Yáñez-Cuna JO, Amendola M, van Ruiten MS, Krijger PHL, Teunissen H, Medema RH, van Steensel B, Brummelkamp TR, de Wit E, Rowland BD. The cohesin release factor WAPL restricts chromatin loop extension. Cell. 2017 169(4):693-707.

【Term of Project】 FY2017-2021
【Budget Allocation】 150,900 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.nibiohn.go.jp/