

EPIGENETICS OF INFLUENZA VIRUS INFECTIONS

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What is Epigenetics?

The term epigenetics refers to heritable changes in gene expression (active versus inactive genes) that does not involve changes to the underlying DNA sequence; a change in phenotype without a change in genotype.

Current known systems considered to initiate and sustain epigenetic changes are:

DNA methylation is a biochemical process where a methyl group is added to DNA nucleotides, stably altering the expression levels of genes.

Histone modifications (e.g. Acetylation, methylation, phosphorylation, sumolation) are the common epigenetic alterations in which histone proteins that package DNA into chromosomes are modified by addition of acetyl or methyl groups.

non-coding RNA (ncRNA) (e.g. microRNAs, short interfering RNAs and piwi-interacting RNAs) are functional RNA molecules that are transcribed from DNA but are not translated into proteins.

All mentioned epigenetic changes regulate gene expression at the transcriptional and/or post-transcriptional level and involve in epigenetic processes such as DNA methylation targeting, heterochromatin formation, histone modification, and gene silencing.

Influenza A virus (IAV) belongs to orthomyxovirus

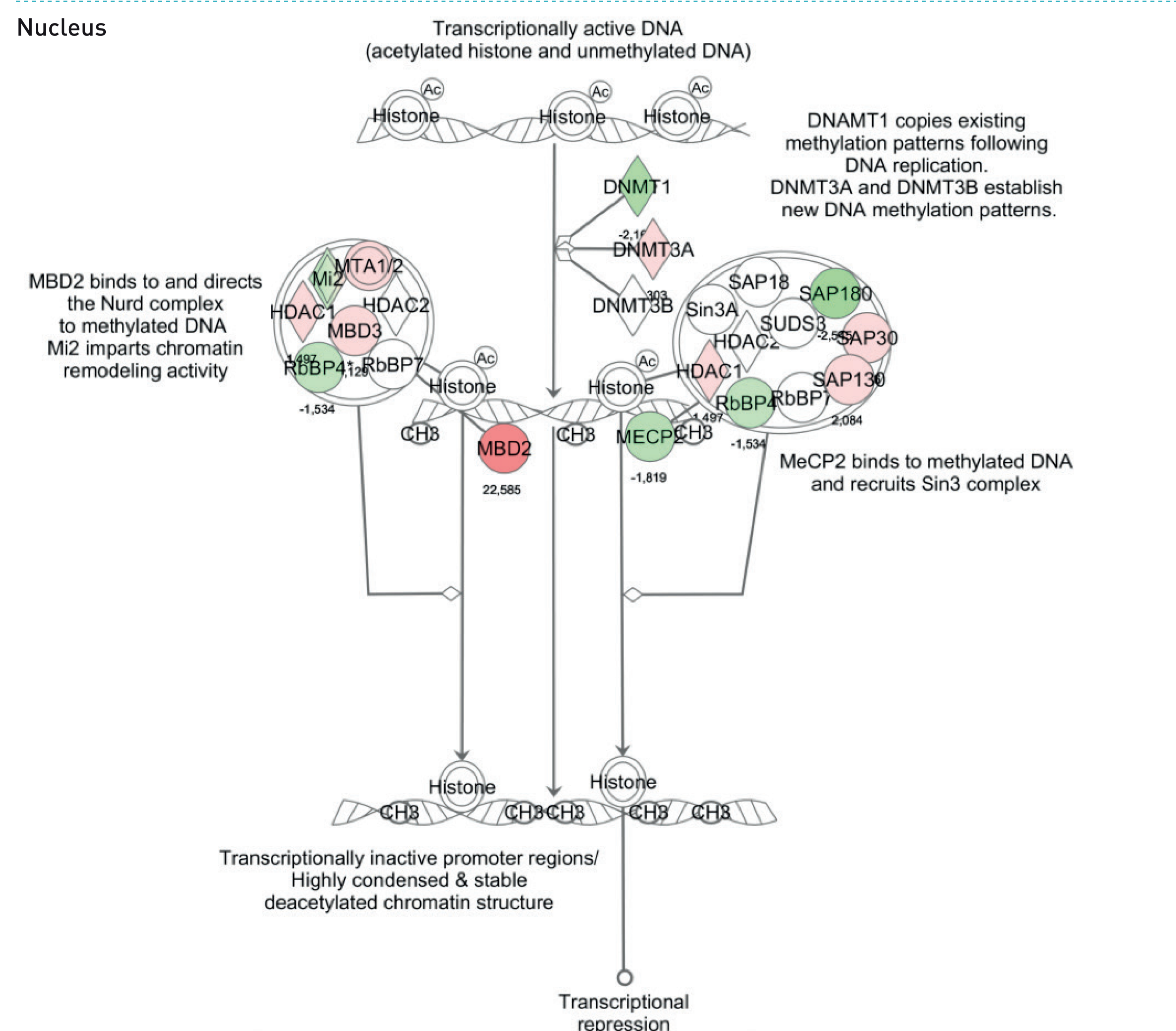
Annual influenza epidemics cause 3-5 million cases of severe illness and 250-500 thousand deaths

every year around the world in human population and important losses in the poultry industry. The most notorious Influenza H1N1 pandemic was the Spanish flu which killed millions of people in 1918-1920.

More recent outbreaks were an avian strain H5N1 which caused Bird Flu in 2004. The novel flu strain H1N1 which caused Swine Flu in 2009, which evolved from combined genes from human, pig, and

Cytoplasm

Nucleus



In silico modelling of DNA methylation and transcriptional repression signaling in H1N1 in vitro infection.

Ingenuity Pathway Analysis (IPA) demonstrates regulation of DNA methylation pathway during in vivo IAV infection. Genes depicted in red are increased and genes in green are decreased compared to mock-infected mice. Colour intensity increases with the magnitude of fold-change.

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*Our genetic code is not Destiny!
The discoveries in epigenetics may rewrite
the rules of disease, heredity, and identity*

PROJECT

Rationale and Objectives

Understanding of epigenetic mechanisms in relation to infection diseases is crucial before any disease prediction, prevention and effective drug design strategies. In Influenza the consequences of epigenetic processes are still under discussion. Influenza viruses are masters at circumventing their hosts' defenses. They co-opt cellular protein-synthesis pathways to produce viral proteins. By hijacking this regulatory machinery, the virus inhibits the cell's production of antiviral proteins.

The objective of this project is to investigate if epigenetic modulations could be associated with influenza virus infection using H1N1 and H5N1 viruses. This may lead to finding markers for innate and acquired protection to infection, which can be used to combat the virus.

Research Questions

- 1- Does an influenza virus infected cell or an infected host retain, acquire or modulate epigenetic markers?
- 2- How does the epigenetic status effect the host cell sensitivity to infection?
- 3- Are there certain epigenetic modifications induced by infection which are essential to virus replication?
- 4- Do these modifications reveal protection markers which can then be blocked to protect the cells?

Methodology

Epigenetic markers will be analyzed during the course of infection in both in vitro and in vivo models.

The modulation of the epigenetic status of the immune cells will be characterized by DNA microarray hybridizations, chromatin immunoprecipitations and mass spectrometry analyses.

Subsequently, we will determine in vitro if epigenetic phenomena interfere with the virus replication cycle in the absence or presence of epigenetic enzyme inhibitors. This will be confirmed by the use of knockout cells for epigenetic enzymes.

Finally, we will try to unravel the effect of epigenetic markers on the acquired protective immunity in mouse infection models using epigenetic enzyme inhibitors.

Collaborators

The French National Institute for Agricultural Research (INRA) - France Producing scientific knowledge and working for economic and social innovation in the areas of food, agriculture and the environment.

INRA Unité de Virologie et Immunologie moléculaires (UR892)

ACIBADEM UNIVERSITY (ACU) - Turkey

A Thematic University on Healthcare

Department of Medical Microbiology and Infectious Diseases

Wageningen University (WUR) - The Netherlands

Focuses on the theme 'healthy food and living environment'

Laboratory of Biochemistry

Further reading

Avian influenza ("bird flu") fact sheet. WHO.

http://www.who.int/mediacentre/factsheets/avian_influenza/en/

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