Review of: "[Review] Dr Jekyll and Mr Hyde: From Two Branches of Immune Response to Three Types of Interferon Response"

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How to interpret facts if there is no theory.

I decided to write a review of the article “Dr. Jekyll and Mr. Hyde: From Two Branches of the Immune Response to Three Types of Interferon Response,” probably primarily because of the title.

However, despite the gigantic literature review presented, I was somewhat disappointed by this review. In my opinion, the purpose of such reviews should be to convey to the general public those new facts that will illuminate the action of interferons and help doctors and scientists study and use them in new ways.

According to the interferome website (http://interferome.its.monash.edu.au/interferome/site/dbStat.jspx), interferons significantly change the work of more than 12 thousand genes, and trying to describe all these changes is almost a Sisyphean task, which is what the author tried to do in your work.

For my part, I want to briefly explain why multicellular organisms needed this additional alarm system. And why does it so strongly influence the functioning of more than half of our genes?

To do this, we need to make a short evolutionary excursion.

According to data based on structural-phylogenomic analysis of self-organizing protein structures (Harish et al, Genome Biol Evol. 2016 Aug 27;8(8):2474-81), viruses have always been companions of cellular life forms and simply chose the parasitic path of development. There is a huge numerical advantage of viruses over cells in the ratio from 1 to 10 to 1 to 100. Their huge number of 10 to the 31st power is simply amazing. How could cells even survive in such an aggressive environment? The first to cope with them were bacteria and archaea, who invented the CRISPR-Cas system, which is their true adaptive immune system. It took almost 2 billion more years for eukaryotic cells, the predecessors of multicellular organisms, to appear. And again, to combat viruses, they changed the antiviral system of bacteria, taking into account the presence of a nuclear membrane and terminal chromosomes. This system is called RNA interference. I have already described this system in detail earlier (Aripova, T., Muratkhodjaev, J. "A novel concept of human antiviral protection: It's all about RNA (Review)". Biomedical Reports 16.4 (2022): 29.). The main thing that needs to be emphasized is that RNA interference is the true antiviral system that every nuclear cell of the human body possesses. It also copes well with ordinary viral invasions. Think for yourself: 100% of all plants and 97% of the entire animal world (that’s how many invertebrates occupy among the described animal species) do not have T and B cells, and accordingly,

they do not have antibodies. But they cope perfectly (judging by the biodiversity of our planet) with viruses. A separate topic is why large vertebrates needed the creation of a specialized immune system in the form of T- and B- cells. And there is only one answer - the fight against cancer. About 1 trillion mutations occur every day in our 40 trillion body alone. By age 60, we accumulate about 130 billion cells with cancer-associated mutations (Evans, E. J., & DeGregori, J. Aging and Cancer, 2021б 2(3), 82 – 97. https://doi.org/10.1002/aac2.12037). This is why we need our specialized immune system, and not at all to fight viruses.

But let's return to the interferon system.

This additional system was necessary for highly organized organisms to quickly respond to viral invasion. The very increase in the number of densely grouped cells of the same type facilitates the spread of viruses - having multiplied in one sensitive cell, virions can easily infect neighboring ones.

Accordingly, innate RNA-guided defenses may not be able to cope with high viral loads. To prevent this possibility, an early warning system was created using interferons as alarm signals.

All nucleated cells have receptors for interferon. After the receptor binds to interferon, many genes are activated and the cell goes into alarm mode, in which the synthesis of protein and nucleic acids practically stops endo- and exocytosis is inhibited, which naturally prevents both the entry and exit of viruses.

Interferon itself is produced by cells into which viruses have already penetrated. Each human cell has a large arsenal of special receptors that recognize certain pathogenic motifs. In the case of viral invasion, there are special cytoplasmic RLR receptors that recognize viral double-stranded RNA. Their activation triggers a whole cascade of intracellular mechanisms, ending with the synthesis of interferons and proinflammatory cytokines. This is all described in detail in the article under review. But let's return to the cells that received a signal in the form of interferon. They go into an antiviral state - the synthesis of proteins and DNA stops, exo- and endocytosis stops, and accordingly the cell does not synthesize viral proteins and does not become infected. This is similar to the behavior of a person who has come under a gas attack - do not breathe and do not get poisoned. But how long can you hold your breath? This is the first one. Second. This also explains the activation of so many genes under the influence of interferons, there is a clear analogy with holding your breath, and I wonder how many genes change their functioning under such conditions. And third. The viruses themselves secrete special molecules that block the activation of not only interferon-induced genes but also block the work of RNA interference. This is all clear, based on the concept of an arms race between viruses and target organisms during coevolution. By the way, it is the presence of such proteins in viruses that once again confirms the antiviral work of RNA interference.

And finally, fourth. Insufficient or delayed production of interferon predisposes to severe viral infection, and its excessive and prolonged synthesis leads to a pro-inflammatory state, cytokine storm, and cell apoptosis. It is these extremes that can be characterized as Dr. Jekyll and Mr. Hyde and would be interesting when considering the work of the interferon system, but in the article, apart from the title, there is no hint of these data.

Thus, many still believe that interferons are a special human antiviral system. It is this interpretation that makes it difficult to understand the true antiviral mechanisms of cell protection, which I briefly described above. And finally, I would like to quote one aphorism from Albert Einstein – «It is the Theory Which Decides What We Can Observe! »