proteinspotlight
> ONE MONTH, ONE PROTEIN <

Issue 246, April 2022
www.proteinspotlight.org

luck of the draw

Vivienne Baillie Gerritsen

When something gets uncomfortably close to you – in whichever way it may be – you will seek to fend it off. By walking away, choosing to ignore it, using physical force or, if it is a person, perhaps verbal abuse. In the same vein, across all kingdoms, organisms have developed a multi-faceted system to fight off the more invisible world of microbial infection: the immune response. The immune response is the arsenal an organism has at its disposal to neutralise invading entities such as viruses or bacteria for instance – and the more complex the organism the more intricate the system seems to be. Despite this, the types of armament provided are only really of two sorts: cells or molecules. Any immune response to infection is an unfathomable combination of both; there being many different kinds of immune cells and myriads of immune molecules. Sometimes, too, genetic inheritance can further fine-tune an individual's reaction to a given infection. In this light, researchers discovered that human individuals who have acquired a specific isoform of a certain protein, known as 2'-5'-oligoadenylate synthetase 1 or OAS1, seem to be less prone to developing the severe form of COVID-19.

Compulsory vaccination drive in New Jersey *ca.* 1880s

National Library of Medicine, USA

The immune response, and its many ramifications, evolved hundreds of millions of years ago with the advent of multicellular organisms. It was a case of letting similar cells cohabitate while preventing the intrusion of outsiders. In short, it was a way of distinguishing the 'self' from the 'non-self'. Nature has been chiseling and refining the immune system ever since but scientists only began to understand the molecular nature of its many components during the last century.

Though it may seem trivial and hardly worth mentioning today, the fact that pathogens – named microbes – could be the cause of certain diseases was only established in the 19th century by the German microbiologist Robert Koch. Now we know that an infection caused by microbes triggers off an immune response that is both cellular and molecular (humoral). We have immune reservoirs – such as our tonsils, our spleen, our liver or our bone marrow – and our blood and lymph ensure that the products are distributed throughout our body.

Surprisingly, although the knowledge we have on the intricacies of the immune reaction is really quite recent, the fact that you can inoculate someone with a disease, in the hope that they will develop some form of future resistance to it, is hundreds of years old. As an example, long before anything of the sort happened in Europe, people in China, Africa and India were being variolated (inoculated) with the smallpox virus – *Variola virus* – to induce immunity. Though many developed a violent reaction and infected others, when an epidemic broke out, the mortality rate in the population was far lower than if no variolation had been performed at all.

The procedure arrived in England in the 18th century. At about the same time, it became apparent that dairy farmers, or indeed their milkmaids, seemed to be preserved from smallpox outbreaks. Little by little, the farmers realised that cow udders infected with cowpox

could in turn infect humans. Cowpox happens to be similar to smallpox, only it is a milder form. Unknowingly, the act of milking cows was actually protecting milkmaids against smallpox. In the 1890s, the English physician Edward Jenner decided to test the hypothesis by presenting the cowpox virus to his gardener's son. Six weeks later, the physician presented the boy with the smallpox virus – who developed no symptoms. Despite this, variolation in Great Britain was only banned from medical practice 40 years later and replaced by Jenner's 'vaccines' – the term given by the doctor himself, meaning 'from a cow'.

Viruses are not organisms and unable to multiply without the help of hosts. This is the basis of infection. Once a virus has entered an organism, it recognizes specific host cells which it will infect. The virus will use the cell's resources to replicate its genome – sometimes in specialized organelles known as replicative organelles (ORs) – and synthesize all it needs to form its progeny, or virions. An infected cell can release up to hundreds of thousands of virions – each of which, like its parent, will infect another host cell. It is not difficult to grasp, then, that in order to halt such wild replication, the host has to react fast. One reaction is to produce small cell-signaling molecules known as cytokines that will trigger the expression of all sorts of genes involved in the immune response.

Once such cytokine is known as interferon. It is the most powerful antiviral cytokine and, rapidly deployed after infection, it activates, among other proteins, the synthesis of the 2'-5'-oligoadenylate synthetase (or OAS) family. This particular family of enzymes is able to sense foreign nucleic acid in the cell – such as viral RNA. Binding to the nucleic acid leads OAS to synthesize 2'-5' oligoadenylates which go on to activate an endoribonuclease (RNase L) that will degrade the viral RNA. In this way, the synthesis of viral proteins is prevented and the early spread of the virus kept at bay. As the now infamous COVID-19 continues to spread around the globe, scientists have had time to observe its mechanics more closely and they made an intriguing discovery: a particular isoform of the OAS family – OAS1 – seems to be involved in saving patients from developing a severe form of COVID-19.

How? OAS1 exists in a short and a long form. The long form, known as p46 and thought to be of Neanderthal provenance, is less common. It has a tail at its C-terminal that encodes for a prenylation signal – a signal believed to facilitate the attachment of proteins to cellular membranes, among which ORs. When severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infects cells, it generates ORs. The viral double-stranded RNAs are lodged within the OR membranes and are immediately, and specifically, sensed by OAS1. Once docked, OAS1 synthesizes 2'-5' oligoadenylates that go on to activate a downstream RNase L that degrades the viral RNA – thus checking viral replication. It seems, therefore, that prenylated OAS1 is specifically targeted to the ORs of SARS-CoV-2, and patients with this particular isoform are less prone to developing complications due to COVID-19 because they can fight it off better.

Naturally, it is very likely that OAS1 is only one of many proteins whose synthesis is stimulated by interferon and it is therefore probably not alone in preventing an acute form of COVID-19. What is more, members of the OAS family are upregulated in the presence of other viruses, as well as in certain autoimmune diseases. Now we know that the long or the short form of OAS1 can behave differently upon SARS-CoV-2 infection, it may be that members of the OAS family behave differently in other disorders too, making them useful biomarkers at different stages of a disease thus prompting development-related therapy. Certainly, scientists have reached a very attractive hypothesis: a gene we might have inherited from the Neanderthals and which may protect many of us from developing a potent form of COVID-19.

Cross-references to UniProt

2'-5'-oligoadenylate synthase 1, *Homo sapiens* (Human): P00973

References

1. Wickenhagen A., Sugrue E., Lytras S., et al.
   A prenylated dsRNA sensor protects against severe COVID-19
   Science 374 (2021), DOI: 10.1126/science.abj3624
   PMID: 34581622

2. Choi U.Y., Kang J.-S., Hwang Y.S., Kim Y.-J.
   Oligoadenylate synthase-like (OASL) proteins: dual functions and associations with diseases
   Experimental & Molecular Medicine 47 (2014), DOI: 10.1038/emm.2014.110
   PMID: 25744296