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The Virome: Viral Ghost Companion, Virus Wars

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Ghost companion,

Silent presence,

Outer light,

Transcendent radiance

Unseen sheath, Microbe field,

Living slayer and eternal shield,

Each breath,

Life from death.

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One recurring question in medicine is why one patient develops a life-threatening illness while another, with similar risk, will have a limited or benign illness. We cannot as yet predict which patients will develop severe sepsis or endocarditis or other aggressive diseases, such as unstable, rapidly progressive atherosclerosis with attendant acute infarction and increased mortality. Recent studies have discovered that the bacterial microbiome acts as a basis for maintaining normal health, but when it is altered or in an unbalanced state, it can cause increased susceptibility to infection and disease. The bacteria that form our outer and inner symbiotic microbial shells produce a complex, interactive and living protoplasm, the bacterial microbiome, which is generally referred to simply as the microbiome for bacteria. In man the microbiome can modify immune responses and susceptibility to disease. Alongside this bacterial overcoat, we would suggest that the virome, or more simply the viral biome to which we are host, will also have a role in altering immune responses [1]. The combined genome that includes bacterial and viral genetic material in a natural symbiotic ecosystem is referred to as the metagenome. (Fungal genetic material also contributes but we will not be discussing a fungal biome here).

An ongoing negotiation, and sometimes a battle, takes place on and in our bodies, on the outer and inner surfaces of all mammals. This microbial populace living on our outer skin and the inner lining of oral and intestinal layers and the respiratory tract interact, and in turn, change or perhaps even direct immune responses to outside threats. This unseen microbe populace, bacterial and viral, determines our ability to respond to invading foreign or non-host pathogens with the potential to prevent, or conversely, encourage invasion and disease by other organisms. This microbial shell, both inner and outer, is composed of both virus and bacteria and represents at least tenfold more genetic material than our own human DNA. One would suspect in general that the bacteria work outside cells through receptors, with some exceptions such as the mycoplasma, and that viruses work as intracellular agents, or even as intra-bacterial agents (bacteriophages).

While the bacterial microbiome has been intensively investigated in recent studies, the extant viral load, the virome, colonizing the host is less well defined. As noted, one can predict that this viral protoplasm, similarly to the bacterial microbiome, will also modify host immune responses. An altered bacterial population, the composition of the bacterial microbiota, is reported to alter susceptibility to upper respiratory influenza infections. Changes in bacterial populations in the gut can similarly cause chronic intractable diarrhea and malabsorption [2,3]. In order to treat foreign invading bacteria, or perhaps to treat just a simple imbalance in native bacterial pathogens in the gastrointestinal tract, or pathogenic bacterial infestations in the gut, fecal transplants using implants of more normal gut bacterial composition into a dysfunctional gut have been used successfully to restore microbial balance and to improve host health. We would propose that, quite logically, the viral populace in a host can also alter susceptibility to other viral infections and possibly also to bacterial, fungal or parasitic infections [4]. Thus, as noted by Virgin et al., these viral and bacterial microbes can be dangerous, benign or protective (symbiotic) passengers on or in the human body. Microbes are everywhere and no part of the human body, including the brain with loss of an intact blood-brain barrier, is immune to microbes.

Based on the premise of 'survival of the fittest microorganism', we have postulated that one invading virus may compete with other viral invaders or even the native viral population, acting to overthrow the native viral symbiots. Conversely, the native viral populace may protect their growing fields (cells) against insurgent viruses or other microbes. This microcosm of viruses, the viral biota, may compete for space and host cells to invade and may even mimic the capacity of molds, such as Pencillium (first identified by Alexander Fleming), which secretes the antibiotic penicillin and blocks surrounding bacterial growth. There may thus be an ongoing battle between viral strains that vie for supremacy, a phenomenon termed here as Virus Wars. Other researchers have detected altered capacity for one virus to proliferate in the presence of differing viral infections [5].

While researchers have demonstrated that some viruses can act

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to support growth of other viruses, as for selected cancer viruses and the mouse mammary tumor virus, we would suggest that viruses, like other microorganisms, compete for territory and host cells in the human body, more specifically in the microbiome or virome. Thus selected viruses may have developed mechanisms through which they can block other viruses from proliferating and spreading. These viral aggressors may interfere with, or actively inhibit, infection by other viruses simply through camping out in a host cell and taking over the cellular machinery for their own purposes of growth and proliferation. Alternatively a virus may block host immune responses that are directed against the initial invading virus (the first invader), which may in turn interfere with other viral invaders that use the host immune response cells to migrate throughout a host animal. One virus may also produce or even secrete agents that can directly block the active spread or proliferation of other viral families. Taking this further a virus may conceivably block invasion by insurgent bacteria or fungi that represent potential competitors for space and resources.

In recent work we have detected marked anti-inflammatory properties for many large DNA viruses, e.g. poxvirus and herpes viruses [6]. These anti-inflammatory functions are extremely potent, often functioning at picogram or even lower concentrations with marked efficiency. Other invading organisms such as bacteria and even the protozoan parasite Plasmodium malariae are also reported to modify host immune responses. Oral bacteria causing oral gingival and carious infections can modify host susceptibility to bacterial infection of cardiac valves and have also been linked to increased risk for atherosclerotic vascular disease [7], as for atherogenesis during Streptococcus mutans OMZ175 infection in ApoEnull mice [8]. The oral virome is also beginning to be noticed (Ly M, et al. mBio.2014; 5: e01133-14). One viral infection exemplar is influenza, for which newer data has demonstrated that vaccination reduces associated risk for cardiovascular disease [9]. Other researchers have detected altered susceptibility to autoimmune disorders such as multiple sclerosis, inflammatory bowel disease, systemic arthritis and lupus, or even asthma, with changes in the metagenome and specifically the virome. Whether this is due to direct vascular tissue invasion or a more subtle modification of host inflammatory and immune responses remains unknown.

The Myxomavirus is a lethal rabbit poxvirus that kills European rabbits rapidly. Mouse herpes virus 68 (MHV68), is a lethal invasive herpesvirus infection in interferon gamma receptor knock out mouse models. Both viruses produce highly potent immune-modulating agents. Our lab, together with others, has reported on these potent anti-inflammatory actions for selected virus-derived proteins when used to treat animal models of vascular disease and even arthritis. The myxomavirus itself has also been used as a selective oncolytic agent. A swinepox virus was introduced in a porcine atherosclerosis model with reported suppression of atherosclerotic plaque growth [10]. However, a surprising finding has been that when MHV68 infected mice were treated with the Myxomavirus-derived anti-inflammatory serine protease inhibitor (serpin), Serp-1, there was not only a suppression of arterial inflammation, but also significantly improved survival [11]. This improved survival was associated with reduced viral load in affected tissues in addition to reduced systemic, arterial, pulmonary, and gastrointestinal (GI) tract inflammation. In a prior pilot study Serp-1 treatment also improved mouse Ebola virus survival as well as again reducing viral load and organ damage. This inhibition of viral proliferation and spread of unrelated viral infections by immune modifying agents produced by the Myxomavirus serpin, is accompanied by a marked reduction in vascular inflammation. This anti-viral activity was only detected *in vivo* and not *in vitro* in pure tissue cultures. Whether this virus-derived anti-inflammatory serpin is blocking proliferation and spread of other viruses via simple interference with immune responses or via a more direct anti-viral strategy, however, remains to be determined.

While not a definitive proof, this data suggests that viruses can use their immunomodulating capacities to block invasion and proliferation of competing viruses. This work would also suggest that viruses, similarly to bacteria, can exist as chronic commensal long-lived infectious processes and not as obligate pathogenic and disease causing infections. Several myxoma and herpesvirus-derived anti-inflammatory agents have been described and studies from a variety of labs have demonstrated reduced inflammation and plaque growth after arterial surgery such as angioplasty or after organ transplant and even in arthritis models. One cannot as yet state whether this inter-viral interaction represents either 1) an alteration of the host immune response that encourages, or prevents, invasion or infection by a foreign virus or 2) a direct virus-to-virus mediated anti-viral action. In other words, does virus-mediated immune modulation make a host more, or less, susceptible to another viral infection or is this rather a direct assault of one virus species on another. Our own work with MHV68 infections, which were modified with Myxomavirus-derived Serp-1 treatment, demonstrated both reduced detectable viral antigen and also reduced macrophage invasion. In mouse Ebola infection, a reduction in viral equivalents was also seen. Certainly other viruses such as MHV68 herpes, other herpesviruses (CMV, EBV and HSV), polyoma and HIV, among others, can chronically inhabit macrophage and T and B cells and alter immune or inflammatory responsiveness of the host cells.

Thus the answer to the question posed at the beginning of this editorial, why do some patients develop deadly disease while others do not, may lie in the immune modifying nature of the symbiotic microbes with which we share our lives. Studies on the virome and its role in host immune defences have the potential to provide new insight into effects of viral infections on responses to external infections. This may open up new fields of investigation into host immune and inflammatory responses and the selective pathways that drive these responses. Investigation into potential roles of other symbiotic organisms contributing to the metagenome, such as fungi or parasites, has received even less attention. This research may lead to new discoveries in immune responses in vascular disease or even in more basic viral interactions that modify host susceptibility to invading pathogens. Rather than submitting to a fear of being taken over by an invading virus as in Ray Bradbury's short story, „Fever Dream" [12], we would suggest that further investigation into virus-mediated immunomodulation and into the virome as an immune-modulating element should be encouraged. Ongoing research on the virome and its modification of host immune responses has extraordinary potential to provide extensive new insights into cardiovascular diseases or indeed any pathogenic process.

Silent host, Extant screen

Outer ghost, Unknown dream

Microbe shell, Fragile chrome

Deeper well, Life's biome

Phosphorescent, Roiling seas

Unseen presence, Viral trees

Life untold, Inner war,

Open soul, Mystic door

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