

Editorial

About Viruses, the Importance of Being Earnest

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When in 1894 Oscar Wilde wrote that “the truth is rarely pure and never simple” [1] he certainly did not have in mind the vast universe of viruses we nowadays recognize, whose stunning complexity keeps amazing us every day. When we think about all the viruses we have discovered so far, about their diversity in shapes, pathogenicity and replication strategies, their various evolutionary behaviors and hosts-interaction tactics, we realize that the truth about viruses is indeed not pure and definitively not simple. Understanding and revealing this truth is a complicated process which requires a constant effort and a lot of energy.

Viral metagenomic studies, broadly diffused also thanks to the noteworthy technological improvements we experienced in recent years, are enlightening us about a great viral world whose existence we could only suspect before. We now know that complex viral communities – formed by both resident and transient viruses – exist everywhere and on every bodily district, and we suppose that these communities have a big influence on our life. This means that alterations of the equilibrium of some of these systems might have relevant consequences on our health, and it is therefore our mission to learn from them as much as possible and use the acquired information to our advantage.

It is rarely pure

Of particular relevance is the ever-expanding knowledge we are acquiring about the human virome, the complexity of viruses encompassing communities all over the human body [2]. Every specific bodily niche is characterized by distinctive viral populations – with their own complexity and dynamics – which count among their ranks a combination of pathogenic, bystander and sometimes even beneficial viruses.

Probably the most intriguing example is the viral complexity of the intestines, whose dynamic composition is constantly changing in response to environmental perturbations [3]. Apart from well-established enteropathogenic viruses, stools enclose a multitude of other viral communities: viruses introduced in the organism with food (e.g. plant viruses [4]), bacteriophages and viruses of parasites, innocuous viruses and a high number of not completely defined viruses [2,5]. An example is the recently classified genus within the *Circoviridae* family: the Gyrovirus. This genus includes viruses identified in both chicken meat and human samples and it is not clear

if these viruses can replicate in humans – and should therefore be considered able of cross-species transmission – or if they are harmless and simply introduced in the body with food [6]. Gut virome studies are also revealing details about the massive presence of bacteriophages [3], and emphasize our limited knowledge about the multitude of possible existing phage types, with many novel viruses waiting to be discovered [7]. The huge genetic distance possessed by these viruses from known reference genomes can make their recognition very difficult, and even more complicated is to identify their host and their function [7].

Also other bodily sites are colonized by microbiological niches which include non-pathogenic viral populations. The surface of the skin, for example, is persistently colonized by viruses (e.g. papillomaviruses, polyomaviruses or circoviruses [8–10]) which are generally innocuous, unless certain conditions are fulfilled, like in the case of the Merkel cell polyomavirus, which is associated with severe forms of skin carcinoma but is also found on the cutaneous surface of healthy subjects [8]. Furthermore, the substantial presence of anelloviruses in blood gives an instance of established clinically silent viruses which colonize our circulatory system [11], while the flavivirus GBVC (or hepatitis G virus) beautifully illustrates how a virus might have a beneficial effect, since it may result in delaying HIV disease progression [12]. Finally, the viral composition of the respiratory tract is again complicated and can be compared to the one of the gastrointestinal tract. The mucosa of our respiratory system, in fact, contains a great assortment of viruses which varies from well established respiratory pathogens (like influenza viruses, corona viruses and many other) to viruses with a still unclear pathogenic role [13], but includes also a great variety of bacteriophages [14] and viruses without any pathological context [15].

It is never simple

In this intricate scenario of a viral Babel Tower, which is strikingly specific in each of its parts, it is fundamental to be able to discern all the possible different viral categories and define the exact effect that each category has (or might have) on human health.

Differentiating passengers from pathogens might be a tough mission in some cases, especially when a “novel” virus is discovered and needs to be fully characterized. We know, for example, that human enteroviruses are implicated in gastrointestinal illnesses but they can also be found in stool of healthy individuals [16], and the same ambivalence can be observed for certain viruses identifiable in the respiratory tract, like the case of the recently discovered human Bocavirus [17]. If these viruses in healthy individuals represent transient asymptomatic infections and are rapidly cleared from the organism or a persistent shedding protracted after the resolution of symptoms can be challenging to establish [14]. Another possibility is that some of these viruses are just accidentally present in our organism and have no relevant effect on our health [6,15].

In case of long-incubating diseases, it is almost impossible to identify the causative pathogen when symptoms appear years after

viral clearance and it is also not simple to recognize which is the role – if any – of a virus identified during disease manifestation. An example are the recently reported high frequencies of parvoviruses in cancer patients [18]: these viruses might be a co-causative factor during the tumorigenic process as well as the effect of it (e.g. reactivation of latent forms). In other circumstances, especially when completely novel viral genomes are discovered, it might be complicated to recognize which is the real host of the virus. This is particularly true for viruses colonizing highly complex systems – like the gastrointestinal or the respiratory tracts – where discriminating between a human virus and a phage can be rather complicated [19].

The importance of being earnest

Nevertheless, every single inhabitant of these communities has its own function, whatever big or small impact it might have on our life and health, and acquiring a more complete knowledge of these microbiological niches is important for multiple reasons. It is obviously crucial when potentially (highly) pathogenic viruses are involved, especially after a new viral emergence [20], to define their pathogenetic mechanisms if we want to develop appropriate cures. On the other hand, some viruses may indirectly influence our health, for example by strengthening our immune response against pathogenic viruses [21], helping us fighting against tumor cells [22] or other infections [12], conferring pathogenic properties to bacteria [23], and maybe in other not yet understood ways. Besides, the importance of knowing the entire diversity of phages colonizing our body is not only relevant because it allow us to clearly and immediately make a distinction between what is a human and what is a non-human pathogen, but also because of the potential therapeutic employment of their antibacterial properties [24]. It is only by investigating all these organisms and how they function and interact with their environment and hosts that new horizons will be visible and future opportunities to positively influence our health will come in reach.

The availability of ever-improving new technologies made the acquisition of knowledge faster and more efficient. We are still at the beginning of our path towards obtaining a full understanding of the entire viral complexity around us, and our mission for the future is to walk this path as far as possible: comprehend every aspect of the human virome will give us new tools to use microorganisms to our advantage.

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