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Viral ageing as a source of evolutionary perspectives: Hypotheses, analysis and methodology

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Abstract

According to the epigenetic theory of ageing, organisms that depend on epigenetic programs for their growth, reproduction, or survival would be doomed to old age due to irreversible losses of epigenetic signals and, therefore, optimal cellular and organ function. Beyond cellular organisms, viruses are also evolved biological entities, as many aspects of their functioning can be explained by natural selection and the use of epigenetic systems. For this reason, viruses have recently been proposed as candidates that interfere with ageing, unless they have developed ways to correct the loss of epigenetic signals. Likewise, for Andean people, time is not something that escapes, but something that is cultivated. They called it Pacha, which means time and space at the same time. The weave of everything that exists means living reality, and when that weave is shaken, reality changes its form. It's not an end, but a reconfiguration. It's not a collapse but a reordering. In this context, we will delve into the analysis and interrelation of available information to propose a methodology that enables the study of viral aging and its implications as a source of new knowledge.

Keywords: Aging; Epigenetics; Evolution; Virus; Carrageenan; Philosophy

1. Introduction

Viruses, despite their obligate parasitic nature, are the most adaptable biological entities, surpassing cellular life in their variability and adaptability. In this way, we could consider viruses as environmental computational messengers that transport, accumulate, and share new codes along their evolutionary paths. Metaphorically, we could see them as seeds that, when finding fertile ground, initiate their life circle or go unnoticed depending on the cellular territory or host. Continuing with the analogy, seen from great heights or immense magnifications, the human population could be seen as seeds, first in the maternal womb and then on earth, simulating a great planetary cell. For both populations, viral and human, many studies exist on their nature, functions, purposes, however, there are few contributions that could provide knowledge about the cycles of entropic dysfunction, such as viral aging, in a system or organism. Historically, since we departed from the sense of unity with mother earth, we have acquired a lot of information and knowledge, prioritizing the rational, material, separation and technology. This has enabled us to be prepared for new integrative proposals with a greater awareness of nature and all life, where viruses are recognized and incorporated. In this study, we analyze, describe, and reflect on viruses, their hypothetical aging, and propose a methodology for their study and contribution to an intimate connection of their forms in the tree of life [1].

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1.1. Time, dance of cycles we have forgotten to observe

In the Andes, the idea of time doesn't have a flat linear shape, but a spiral one. It's not about progressing towards the unknown, but about rotating with the known from a deeper place. Ancestral people knew that time was not something that escapes, but something that is cultivated. They call it PACHA, but PACHA doesn't just mean time or just space, it means both at once. It means the fabric of everything that exists, it means living reality. And when that fabric shakes, when reality changes its form, they call it PACHACUTI, a sacred turn of time. Not an end, but a reconfiguration. Not a collapse, but reordering. In each PACHACUTI, time reminds us that what seems eternal can also turn, and that true order isn't static, it's dynamic. Another profound difference in the Andean worldview is that the past isn't behind, it's ahead. They call it NAUPA, which literally means what's in front of you, because it's what you have already lived, what you can really see, what you know. Instead, the future is called KIPA, what's behind, because you can't see it [2]. You don't know its form yet, it hasn't revealed itself. This way of seeing time changes everything, changes how we act, remember, plan. It forces us to stop running towards the invisible and pay attention to what's already there, what's in front of us, what asks to be understood before we keep spinning. In relation to viruses, they are ubiquitous components of the web life [3]. And the ecological and evolutionary critical roles of viruses are increasingly recognized. Viruses affect the dynamics of their host community from prokaryotes to animals, and possibly impact even biogeochemical cycles [4,5,6]. However, despite this, within the biological world, viruses are currently largely ignored by theories of aging and evolutionary theories of aging. Ancient sages knew that not all movement means progress. Not every action is growth. That is way they spoke of KAUSAY which doesn't translate easily. KAUSAY is life, yes, but not just as biological existence. It's vital energy, the living force that in habits everything. In you, in me, in mountains, stones, wind, viruses, the words you use, and the thoughts you carry KAUSAY isn't seen, but it felt. And when we live disconnected from it, walking becomes noise, actions lose their roots, time becomes dry, and it distances us from the invisible fabric that unites us with everything that exists [7]. This is what's perceived. current evolutionary theories on aging don't explicitly consider the countless interspecific and ecological interactions increasingly recognized as responsible for the evolution of organisms. Every step of action we take can alter that fabric; every word can strengthen or damage it. Haste makes us clumpy; awareness makes us part of it. That is why walking with KAUSAY is living with presence, and knowing it isn't enough, you have got to live it. In the Andean worldview, learning about time doesn't come from abstraction, but from observing natural cycles. Time doesn't shout, it whispers, but only those who don't run hear it. In this way aging is a natural result of an evolutionary time. To maintain their identity and functions, cells and organisms depend on evolved biological processes capable of preserving their information content for a certain time, in the face of natural dysfunction. Beyond cellular organisms, viruses are also evolved biological entities, as many aspects of their viral functioning can be explained by natural selection and the use of epigenetic information systems for the optimal completion of their replication and persistence cycle, what isn't seen, repeats itself. And what is seen transforms. For that, you need to stop, create space, let time surround us, and not just pass over us. Time doesn't impose itself. That's the wisdom of time, tenuous but constant. And in that listening, we discover that time is also memory. Not as an accumulation of data, but as resonance. The past isn't a dead archive, it's a vibration that remains alive in the present time, each gene, each Word of an elder, each microorganism, each transposon, each footprint on the path is a site that holds a time, a time that's not measured but felt. The memory of Andean time isn't nostalgia, its root. It reminds us that everything that was still is, but with another name, in another form. And only those who honor what once was, can receive what's to come. The recent development of epigenetic theories of ageing suggests that even viruses age too, meaning they present an increasing risk of not completing their individual life cycle and disappearing over time. This ageing process leads to significant epigenetic changes at all levels of chromatin and DNA organization [1]. Time doesn't respond to urgency. It responds to coherence of your steps, and when you walk with rhythm, your body, words, actions, and silence respect that beat, everything starts to flourish. Not through haste, but through maturation.

2. The epigenetic theory of ageing

The epigenetic theory of ageing (ETA) states that to avoid ageing as a consequence of the loss of critical epigenetically encoded functions, any system relying on epigenetics must ensure sufficient epigenetic fidelity throughout its lifespan [8]. Indeed, unless epigenetic damage, (for example gain or loss of a methyl group along DNA molecule), can be faithfully repaired, it will result in loss of information. Duffield and collaborators argue that particularly cells of complex multicellular eukaryotic organisms are, unfortunately, unlikely to contain such solutions [9]. Importantly, multicellular organisms aren't the only biological entities relying heavily on epigenetic information for optimal functioning. Many microbes, bacteria, archaea, protists (unicellular eukaryotes), and beyond these cellular life forms, viruses use epigenetic information for their normal functioning. Thus, Duffield and Col propose that an epigenetic signal repair system could be encoded using a biological system with a more immediately accessible memory and possibly broader storage capacity than DNA [9].

2.1. Host virus interactions and epigenetics

Recently, viruses have been proposed as candidates that interfere with the ageing of their hosts. According to ETA, organisms relying on epigenetic programs for growth, reproduction, or survival would be doomed to old age because epigenetic signals can only be lost irreversibly, and therefore optimal cellular, and by extension, organismal functioning cannot be maintained indefinitely. Therefore, unless viruses using epigenetic signals for their normal functioning have developed ways to correct their loss or epigenetic signals, the above considerations make them victims of such loss and Detrimental dysfunctions [10,11]. Furthermore, according to classical evolutionary theories of ageing, the older mammalian host gets, the less efficiently any host repair system is likely to function [12,13]. Therefore, viral reactivation in an aged host may reflect failure to maintain an optimal long-term survival strategy for a virus, and as such may appear as a manifestation of viral ageing rather than preserved functionality. The evolutionary benefits of viral reactivation are still unclear, and some authors have suggested that reactivation in elderly hosts may not be part of a selected strategy for the virus [14]. In the case of herpes simplex virus (HSV-1), infection, a virus not considered oncogenic but that can increase the risk of malignant progression, latency also appears as an adaptive phenotype allowing the virus to escape the hosts immune response [15]. So, it's possible reactivation isn't advantageous for these viruses. Aged infected host cells should contain more defective viruses over time, while non- defective resident viruses could still reactivate because the hosts immune system is weaker, these reactivations may originate from viral populations increasingly loaded with defective viruses, thus involving aged virus populations.

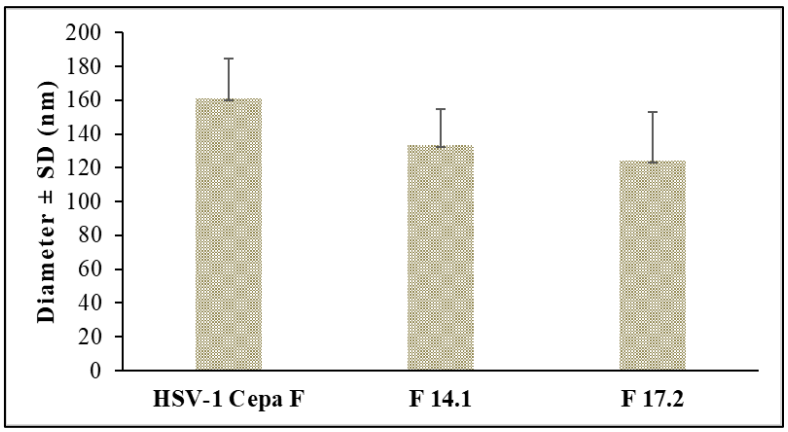
2.2. Possible benefits to studying aged viruses

If viruses within a host or in the environment present an increasing risk of failing to complete their life cycles by becoming defective, failing to replicate, and or disappearing over time due to loss of epigenetic information, this viral ageing phenotype would be worth studying with experimental models to improve explanations of viral dynamics both in nature and in infected host genomes. According to the notion that some viruses age, viruses integrated into their hosts DNA often fail to complete their viral cycle, and their hosts genomes become their graves, perhaps because some viruses have become epigenetically old [8]. Discovering epigenetic ageing in some viruses could also have the potential to reveal efficient, unknown viral epigenetic repair systems. An alternative evolutionary solution would be that viruses have developed more reliable alternative forms of epigenetic regulation if the DNA sites with epigenetic information suspected of contributing to mammalian ageing were located in part in genes of viral origin long inserted within their host genomes or came from other evolving but non-living molecular travelers like transposons, epigenomic profiles could be generated for various viral populations from viruses cultured in a range of culture conditions. Such epigenomic profiles could be compared across different cultural conditions, (for example, to assess whether some distributions are enriched in rare epigenetic variants) and to correlate proportions of various epigenetic marks with proportions of genetic mutations in the populations analyzed. No doubt, the epigenetic regulation of a diversity of viruses (e.g gamma herpes viruses like EBV, HIV, etc) and their hosts can be interconnected [16,17, 18,19,20,21]. So, mammalian epigenetic ageing could have an infectious origin. Ancient infections, infections that occurred before an organism's birth, e.g, an infection resulting in long-term insertion of viral sequences into a host lineages genome, could theoretically be involved in the later developments of animal epigenetic ageing. In humans, the main suspects are Human Endogenous Retroviruses, known to influence transcription of our genes, possibly through epigenetic interference [22]. Basically, viral infection is known to change the epigenetic profile of the infected host, as integration of foreign DNA can lead to changes in DNA methylation and transcription patterns in mammalian cells [23]. If this hypothesis is correct, loss of epigenetic information would have been one of the first causes of ageing to appear in nature, possibly alongside loss of proteostasis [24]. On the other hand, other possible ageing mechanisms, e.g. cellular senescence, mitochondrial dysfunction etc, would have evolved later.

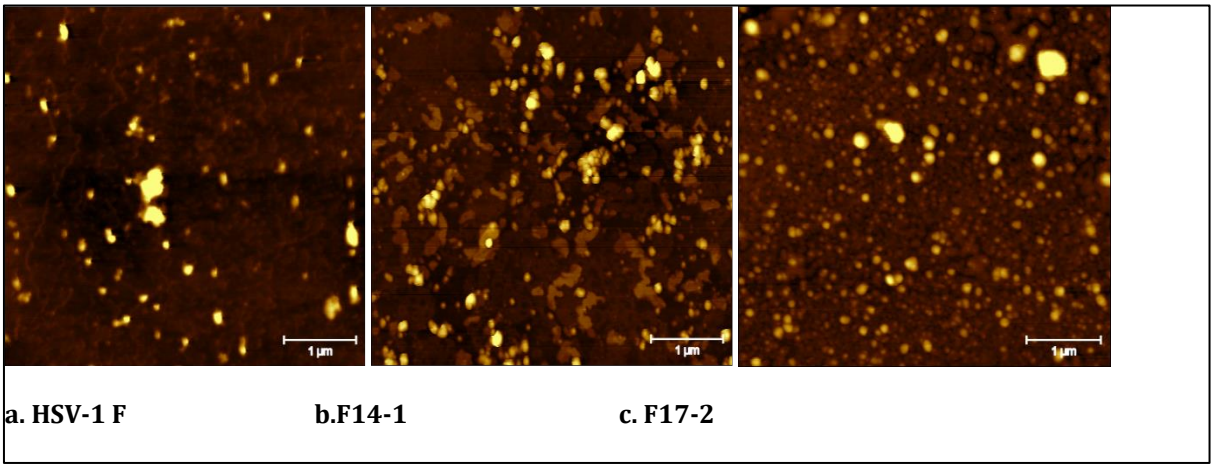
2.3. Proposed model for discovering viruses aged by epigenetic signal losses

Our proposed methodology involves the interaction of different types of sulphated polysaccharides (with a similar chemical structure to the glycosaminoglycan heteropolysaccharides (GAGs), cell surface and extracellular matrix components known as carrageenans (CGNs) and HSV types 1 and 2 [25]. From successive passages of the virus with increasing micro-doses of said sulphated polysaccharides, viral variants were obtained with multiple differential characteristics compared to the wild strain, such as: different (syncytial) cytopathic action, smaller size with increased passages (Figure 1), attenuated or altered virulence, scarce innate immune response and resistance to CGNs compared to Acyclovir, [26,27,28,29]. The study of mechanism of action of CGN son HSV replication suggests that they would mainly affect the initial absorption stage of the viral cycle, involving surface glycoproteins such as gB, gC, and gD [30,31], and viral DNA polymerase and thymidine kinase are also affected [32]. Likewise, we can infer that these molecular and biological alterations could significantly interfere with viral and cellular RNA networks [33]. Thus, the results obtained support the hypothesis that using viral variants obtained by adapting the virus to multiply in the presence of natural CGNs, could be a possible alternative to study numerous topics, including ageing [34, 35]. This procedure could be

applied to other viruses susceptible to this class of compounds such as cytomegalovirus, Influenza A virus, and respiratory syncytial virus [36, 37, 38], Human immunodeficiency virus (HIV) [39, 40], and against some non-enveloped viruses such as , encephalomyocarditis virus, hepatitis B[41] and Hepatitis A virus [42], with both DNA and RNA genomes.



A



B

Figure 1 A) Viral particle diameter of HSV-1 strain F, passage 14 of strain F with CGN clone 1 (F14-1) and passage 17 of strain F with CGN clone 2 (F17-2), using Gwyddion analysis from manual measurement (to avoid the error associated with background noise). B) Topographic images of viral particles (HSV-1) obtained by AFM, 5µm^2 scan area from which the particle diameter was determined. a) HSV-1 Strain F, b) F14.1, c) F17.2

3. The basis of Methodology

It has been reported that the proteoglycan heparan sulfate, a polysaccharide component of vertebrate cell membranes and extracellular matrices releases soluble heparan sulfate fragments during inflammation and tissue damage [43]. In healthy tissues, no significant fractions of soluble heparan sulfate are found, but they are present at concentrations within the ranges observed to stimulate dendritic cells in fluids from injured tissues [44] and in urine from infected individuals [45]. Likewise, sulphated polysaccharides like CGNs can be incorporated into the body exogenously through diet, pharmaceuticals, or cosmetics. Therefore, this type of viral variant could be generated spontaneously due to the structural similarity of CGNs with cellular heparan sulfate, mainly affecting envelope glycoproteins. In turn, HSV has developed multiple strategic defense skills to be optimally equipped for immune evasion and to respond to host attacks during infection and reactivation. Some of the mechanisms comprise:

- Viral escape through alterations in the viral envelope or reduced viral expression during latency.
- Viral resistance, such as sequential induction of pro- and anti- apoptotic effects in defense cells.

- Viral counterattack by inhibiting dendritic cell maturation [46].

Some determinants for immune evasion are found in the surface glycoproteins (g) of HSV-1, expressed on the viral envelope and on the surface of infected cells. Thus, gB interacts with HLA-DR and HLQ-DM polypeptides, reducing invariant chain expression and disrupting MHCII [47]; gC interferes by evading complement- mediated neutralization. Specifically, gC binds to C3 and activation products C3b, iC3c and blocking the interaction of C5 and properdin with C3b [48]. Similarly, gC is involved in the adhesion of monocytes to endothelial cells [49]; gD induces activation of nuclear factor kB (NF-kB) and protects against apoptosis in the early phase of infection , ensuring a surface for viral replication [46] and also gD uses a cellular surface receptor nectin-1, which belongs to an adhesion molecule of the immunoglobulin family, to facilitate cell entry [50]. So, alterations in these glycoproteins, caused by successive interactions with endogenous, soluble or exogenous microbicidal polysaccharides, could modify their normal behavior, leading to asymptomatic or subclinical infections [51].

4. Discussion

Viral variants obtained by this methodology can be triggered by "environment-sensitive" glycoproteins. These glycoproteins can act by themselves or transmit the stimulus to "adapter "proteins, particularly tegument proteins within the virion, which eventually modulate the expression of genomic products in the "virocells". Modulation of the ARN network is a common strategy of the “virocells” to respond to environmental changes. This "rapid" adaptive mechanism is eventually followed by the emergence of mutations in the viral genome. We interpret these findings by interconnecting the epigenetic action exerted by CGNs, from the early interaction of the ARN-ADN network to the late DNA mutation [33]. The identification of natural chemical structures that have already been in contact with the pathogen throughout its evolutionary path and are widely distributed in nature, as well as being part of essential cellular components, would be an innovative approach. It will allow us to understand the bases of cooperative symbiotic host interactions, as well as those that promote the persistence of information contained in both the genome and other viral macromolecules. To achieve this, research in molecular evolution and evolutionary genomics is fundamental and highly relevant to foster new studies, such as in gerontology, uncovering new viral mechanisms capable of modulating epigenetic aging and rejuvenation; in molecular ecology and genomics, considering new parameters to explain microbial dynamics and pandemics in nature and in host genomes. Current evolutionary theories on aging don’t adequately answer the new questions about “how” and “why”. The molecular pathways evolved associated with ageing. Furthermore, they don’t explicitly consider the countless interspecific and ecological interactions life such as symbioses and host-microbiome associations, increasingly recognized as driving forces behind the evolution of organisms across the life web. However, it’s increasingly recognized that a complex network of interactions connects an organism to its environment, including other organisms [52]. This makes it clearer that epigenetics and its molecular mechanisms represent the physical pathway that gives nature freedom to express itself creatively at its own pace [53].

5. Conclusion

This study aims to contribute renewed evolutionary and epigenetic approaches to reinforce the role of viruses and their aging in the Tree of Life.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential of interest.

Author Contributions

The authors have made a substantial direct and intellectual contribution to the work and approved it for publication. Each author contributed equally to all sections of the manuscript.

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