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Vestigial vigilance: Reactivating dormant evolutionary pathways in human immunity

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Abstract

The article is an innovative approach to studying less understood yet potentially significant evolutionary systems, such as Human Endogenous Retroviruses (HERVs) which constitute approximately 8% of the human genome without known pathogenic consequence and have been previously considered as non-functional DNA, the includes the theory that immune systems, having adapted to ancient environments pressures, may not be optimally adapted to contemporary environments. The article introduces a new paradigm to the research on the poorly understood yet potentially beneficial elements of human genome evolution, including the Human Endogenous Retroviruses (HERVs), which are benignly integrated in 8% of human genome and the long-overlooked hypothesis of suboptimal immune adaptation: immune systems evolved in old environments, which can be poorly adapted to new environmental pressures. The article highlights an evolutionarily conserved form of innate immune memory, known as Trained Immunity, as a target of vaccines and immunomodulators. Careful regulation of this frontier suggests that novel approaches can be developed of treating cancer, and durable treatments of chronic inflammatory diseases in the twenty-first century by integrating evolutionary insights and functional genomics.

Keywords: Vestigial Vigilance; Evolutionary Pathways; HERVs; Trained Immunity

1. Introduction

Human immune system is a complex and ever-changing system of defense that is very carefully crafted to protect the body against a wide range of pathogens and intra body threats.[1] This defensive mechanism has developed over millions of years by environmental forces of selective pressure, such as exposure to microbes at all times, resulting in the existence of both innate and adaptive immune responses.[2] Nonetheless, the contemporary context is very different to that in which our forebears adapted, which can cause an "evolutionary mismatch" with certain immune responses no longer being the most ideal and, in some cases, even becoming disastrous.[3] So, in that, the theory of Vestigial Vigilance can appear as a model of interpreting the aspects of immune-based pathways being dormant or underutilized in our genome that can be re-activated to enrich the human immune system in the case of modern health risks.

Such remnants contain evolutionary genetic building blocks, including Human Endogenous Retroviruses (HERVs) which were previously viewed as junk DNA, but now known to play an important regulatory and immunological part.[4] Such elements may serve as what has been called as the dormant guardians, which can be triggered at certain circumstances to arouse immune responses. Moreover, the knowledge gained about immunity in our classmates and other species may give useful clues as to the key principles of immunity, which have been preserved during evolution.[5]

The purpose of this review article is to discuss the notion of vestigial vigilance of human immunity in relation to three major axes. First, we are going to discuss Human Endogenous Retroviruses (HERVs) as inert remnants of the genome that can serve as dormant sentinels in the immune system, their roles in innate and adaptive immunity, and their potential in medicine.[6] Second, we will explore what our ancestors and other species have taught us, with an emphasis

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on discovering what allows us to be adaptable in response to evolutionary immunology, and on the notion of trained immunity.[7] Lastly, we will incorporate these ideas in order to offer an overall vision of how we can reactivate silenced evolutionary signaling by human immunity which would then open the door to the creation of new immunotherapies that would help unlock the untapped potential that exists within our own genome.[8] The demands of global health, whether it is emerging infectious diseases or chronic illnesses such as cancer and autoimmune diseases require a revision of our immune approaches.[9] Through evolutionary approach, we are able to unravel some of the old but powerful defense mechanisms that can be used to improve human health and well-being in the twenty first century.[10]

2. Human Endogenous Retroviruses (HERVs) as Dormant Guardians

Human Endogenous Retroviruses (HERVs) are integral to the human genome, and they comprise about 8% of human DNA.[11] These viral components are the remnants of ancient retroviral infection**s** which incorporated their genomes in our germline, and have influenced our forebears.[12] Although most of the HERVs have become incapable of replicating due to mutations and deletions, a few others still have functional genes or regulatory elements that can control the activities of host cells.[13] The association between HERVs and the human host has not always been parasitism, but a complex symbiosis in which HERVs have many multidimensional functions in physiology and pathology.[14]

Previously regarded as inactive evolutionary remnants, recent studies have helped to reveal the essential functions of HERVs in the development of the human immune system.[15] Viral proteins or RNA (HERV products) can induce danger-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs), which leads to the activation of innate immune pathways.[16] As an example, the production of pro-inflammatory conditions can be induced by the expression of HERV envelope proteins, which would contribute to the immune response against pathogens or cancer cells. The envelope protein Syncytin-1, a derivative of HERV-W, that functions in a critical manner during the development of the placenta by facilitating trophoblast cell union was one of the most notable demonstrations of the functional role of HERVs.[17] Also, researchers report that HERVs have the potential to modify adaptive immunity, by altering antigen presentation, or mediating T-cell differentiation.[18] Notably, the expression of HERV in cancer cells may render them more immunogenic, and this may open new possibilities in the area of cancer immunotherapy.

Nevertheless, there are negative aspects of the connection between HERVs and immunity. Uncontrolled outbreak of the HERV may cause autoimmune diseases and inflammatory diseases.[19] Activation of the HERV has been found to contribute to disease progression in conditions like multiple sclerosis and systemic lupus erythematosus, by mediating inflammatory effects and tissue destruction. It is important to know how HERV expression is controlled such as through cellular transcription factors, epigenetic modifications and RNA interference to come up with a therapeutic strategy.[13] A targeted reactivation of dormant immune pathways by exploring these regulatory pathways may have the potential to enhance anti-cancer responses or anti-microbial response. The concept of re-establishing genetic relationships between inactive evolutionary routes by the use of HERVs holds potential. Learning about how HERVs become activated in certain disease settings, researchers can design interventions which can be used to manipulate these mechanisms to boost therapeutic immune responses. As an example, triggering cancer cell-based expression of the HERV might result in them being more immunogenic and therefore more vulnerable to immunotherapy.[20] Likewise, the investigation of HERVs potentially developed to immunize against primitive pathogens might identify new antigens with which immunity should be enhanced against modern diseases. Conclusively, the remnants of viruses have transformed into important contributors of the human immunity, into HERVs. Their ability as slumbering guardians, which enables the activation of both innate and adaptive immune responses, is a novel research and treatment possibility. An analysis of the challenging interaction between the HERVs, the human genome and the immune system will be useful in comprehending the evolutionary modalities of the immune system.[21]

3. Lessons from Ancestors and Other Species

The development of the immune system through the fossil record and its evolution across a range of species can provide profound insights into the latent immune routes that may lie dormant in the modern human bein.[5] Millions of years of interaction have given rise to the different and sophisticated immune systems that are also shaped by antagonistic host-pathogen interactions under selective pressure.[22] Understanding these evolutionary adaptations, we can see some basic principles of immunity that can be reactivated or altered in order to improve the health of humans.

Primordial organisms, like bacteria and archaea, have primitive types of immunity, including CRISPR-Cas systems, which defend against viruses adaptively.[23] In invertebrates, e.g. insects, innate immunity has also developed to be their first line of defense and mechanisms such as phagocytosis, antimicrobial peptides and coagulation systems have evolved.[24] These mechanisms are excellent in responding to a large variety of pathogens very rapidly, indicating some

elements of ancestral innate immunity could have been preserved or memory persists in humans. In the development of vertebrates, adaptive immunity developed, which involves immune memory and specificity that also offer a long-term immunity against a specific pathogen.[25] Nevertheless**,** natural immunity did not diminish rather co-evolved together with the adaptative immune system, creating a complex immune system.[26] It has been found that examining species with simpler immune systems, like sharks and rays, which developed adaptive immunity independently can be used to identify the key components required to have an effective immune response.[22] Such evolutionary lessons can facilitate the identification of basic immune pathways, which can be reactivated.

Evolutionary immunological studies have indicated that genes regulating the immune system evolve quickly due to pathogenic selection.[27] Varying levels of immune genes in human populations can arise during historical migrations and evolutionary changes and influence the susceptibility to diseases. An example to illustrate this is that a genetic variation that was once an advantage in the context of ancient pathogens might no longer be helpful in the modern context and become an evolutionary mismatch.[3] The concept can also help to explain why some autoimmune diseases and allergies are common in contemporary communities.

The theory of Trained Immunity, as a type of innate immune memory, offers a strong evidence suggesting that innate immune cells do have the ability to recall earlier experiences and mount a stronger reaction to subsequent infections.[28] This has been found in human beings as well as other species thereby demonstrating its evolutionary conservation. Trained immunity mechanisms may include epigenetic changes that alter the expression of the genes and can enable the quick mediating of immune genes.[29] The mechanism of induction and regulation of trained immunity might provide insights into reactivating dormant immune pathways e.g. by vaccination or immunomodulators directed to inert immune pathways. Moreover, the research of immune responses in long lived species or species living in severe environmental conditions can also provide insights into specific characteristics in disease resistance mechanisms.[23] Indicatively, certain species can have more effective DNA repair systems or high anti-inflammatory immunity to protect them or make them longer-lived and healthier. Such mechanisms, understanding these mechanisms can offer paradigms of the reactivation of protective pathways in human beings.

As a reactivation of previously silent evolutionary pathways, future studies can consider the identification of silenced or altered immune genes or pathways in modern humans, but which are active in other organisms or in ourselves as ancient humans.[10] The possible interventions might involve gene engineering of gene expression, pharmacologic therapies aimed at modulating the epigenetics, or dietary interventions that enable recreating the environmental conditions of our forefathers. It is aimed at using the evolutionary insights inherent in our genomes to increase capacity to combat diseases.

To conclude, the evolutionary approach to immunity offers a wealth of knowledge about the way in which our defense mechanisms have evolved.[30] Examining immunity in our ancestors and other species can reveal any dormant immune pathways that can be useful to humans. This practice involving a combination of immunology and evolutionary biology has tremendous potential to develop novel immunotherapy application as a way of strengthening human immunity and fighting a variety of illnesses.[10]

4. Re-evaluating Their Immunological Role

The human evolutionary genomics information has led to the total reevaluation of the role of Human Endogenous Retroviruses (HERVs) in immunity and the relocation of these molecules as the passive molecular fossils in the immunomodulators.31 Recent data show that these components are not just the evolutionary remnants, but dynamic elements which help to maintain the homeostasis of immune system and react to the biological threats.32 Epigenetic regulations of HERV expression are highly regulated, and involve both epigenetic modification of the DNA (methylation) and repressive histone marks, silencing in old age or in disease conditions, leading to HERV re-expression.33 This stimulation causes the development of double stranded RNA molecules (dsRNA) which act as effective agonists to innate immune sensors like MDA5 and STING, which mimics a true viral infection, this is known as viral mimicry.34 Moreover HERV-derived envelope proteins can play two roles, some of them being capable of causing immunological tolerance (as in the placenta) and others of role in chronic inflammation during aging or inflammation in aging.35 These complex functions provide new insights into the understanding of the phenomenon of the viral heritage in our genome and its impact on our present-day immunity capabilities.36 It is also evidenced that HERVs can be used as regulators of gene transcription networks, which by targeting sites of immune transcription factors, thereby enabling a more dynamic and adaptive immune response to ongoing evolutionary pressures.37

5. Therapeutic Applications: From Defense to Reprogramming

The reactivation of inactive immune pathways, especially with the help of HERVs, is a transformative in regeneration medicine and immune therapy of cancer and a paradigm shift from classical defense mechanisms to reconfiguring the immune response in the host organism.[38] These applications are based on the capacity of induced HERVs to convert the immunological cold tumors into the immunological hot tumors by increasing interferon levels and recruiting cytotoxic T cells into the tumor microenvironment.[39] More recent clinical studies indicate that DNA methyltransferase inhibitors (DNMTis) can increase HERV-K expression, thereby providing novel antigens for personalized cancer vaccines and adoptive cellular therapy.[40] Also, viral envelope proteins are under development as directed antibody targets, and studies indicate that directed antibodies to HERV-K Env protein can prevent growth of solid tumors and aid the effectiveness of currently used immunotherapies.[41] In the context of neurological diseases, approaches are under development to re-program microglia by regulating the activity of HERVs to lessen neuroinflammation and enable tissue repairing.[42] CRISPR/Cas9 gene editing technologies can also be utilized to precisely activate or suppress certain loci of HERV in order to gain precise control over previously inaccessible evolutionary processes.[43] Such a change in perception towards exploiting the genomic viral heritage is expected to present new therapeutic solutions to the diseases that are resistant to the classical methods of treatment, taking advantage of evolutionary wisdom that is encoded in our genome.[20]

6. Challenges and Ethical Considerations

Although the reactivation of dormant immune pathways has a promising future, such mode of practice is fraught with technical and ethical issues that must be taken into account in detail.[44] The largest technical issue is to guarantee the precision of activation; uncontrolled stimulation of HERVs may result in the capacity of the organism to produce a devastating destabilization of the immune system or even induce genomic instability, resulting in a new tumor development rather than in a treatment of the existing one.[6] Moreover, HERV loci are highly variable and thus hard to make uniform therapeutic approaches, and they require a very specific and individualistic approach.[45] Ethically speaking, treatment aimed at inherited genetic factors puts under scrutiny long-term safety concerns and possible impacts on later generations (particularly of gene editing technologies, applied to germline cells or precursors).[46] There are also concerns over cellular infection; and possibilities of virus-like particles following the activation of transferring it to neighboring healthy cells that results in premature senescence or cellular dysfunction.[15] These dangers lead to rigorous regulatory mechanisms and global ethics to make sure that therapeutic gains exceed the possible dangers.[35] One of the pillars has been the tradeoff between scientific innovation and ethical responsibility to develop these technologies in such a way that Vestigial Vigilance is not a producer of new biological hazards but it is a therapeutic tool.[22]

7. Conclusion

The study done on the Vestigial Vigilance is a breakthrough in the study of human immunity. A goldmine and untapped field of therapeutic possibilities, re-evaluating Human Endogenous Retroviruses (HERVs) and other suppressed issues, not as products of evolution but as functional sentinels, by re-evaluating the truth about the human body, the latter can be rediscovered. The revolutionary potentials of the reactivation of these ancient pathways in cancer immunotherapy, regenerative medicine and in the treatment of chronic inflammatory diseases are revolutionary. It is blemished however by the fact that very extreme accuracy is needed in the clinical application road in order to avoid the dangers of autoimmunity and genomic instability. By bridging the gap between evolutionary biology and modern immunology, we in the real sense are learning how to harness the so-called evolutionary wisdom within which millions of years of evolution have toiled. The most burning issue that the modern world is confronted with that the strategy entraps is the extreme incompatibility of evolution, which provides a more reliable defense against the novices and anomalies in the human body. Lastly, it is a collaborative endeavor that requires multidisciplinary solution of integrating effectively and in an unbiased manner these latent pathways into the medical practice without compromising the scientific innovation of the same. Cracking the code of our genomic past, we also bring one step closer to the future where the human immune system will not be merely a product of the past, but the dynamically programmable resource of a healthier 21st century.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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