Editorial

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Human Endogenous Retroviruses: Innate Triggers or Immune Sentinels?

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Editorial

Human Endogenous Retroviruses (HERVs) represent an intriguing encounter between self and non-self, at the interface of human genetics and virology. Acquired over the last 100 millions of years, through consecutive infections of the primates' germ line cells, HERV sequences have been inherited through the offspring in a Mendelian fashion and accounts now for about the 8% of the human genome [1]. In the last decades, driven by the increasing amount of bioinformatics data and tools, a great attention has been dedicated to the study of HERVs and their possible physio-pathological interplay with the host. The latter ranges from the domestication of HERV-derived proteins for important pregnancy related functions [2-4] to the tentative implication of HERV products expressed in a variety of human diseases including cancer [5] and autoimmune disorders [6].

Worth of note, a number of evidences indicate that HERVs are generally tolerated by the host immunity, being albeit able to trigger the host defense systems on occasion. This double effect suggests a delicate balance between the contribution to the host function and the maintenance of a basal immune alert, possibly acting as endogenous sentinels for human defenses, and leading in some conditions to harmful effects. As an example, the expression of HERVs has been proposed to confer an innate protection against exogenous infections. This could occur due to the similarities between the RNAs of HERVs and exogenous retroviruses, eventually leading to the formation of double stranded RNA, a pathogen-associated molecular pattern that is easily detected by innate immunity effectors [7]. At the protein level, another HERV-mediated antiviral effect could rely on their molecular mimicry of exogenous viruses' antigens, leading to receptor interference and conferring resistance to infections [8]. However, expressed HERVs may also generate negative effects to the host. Still regarding exogenous viruses, HERVs can potentially determine cooperative actions, by stimulating exogenous virus transcription or by complementing defective elements [9]. Besides the presence of exogenous elements, HERV products can themselves act as immune triggers, being in fact intensively studied in relation to autoimmune disorders due to the presence of related antigens and/or specific antibodies in patients as compared to healthy individuals [6]. Even in the absence yet of any definitive association between HERVs and autoimmunity, it is interesting to note that, as stable components of primates' genomes since millions of years, an immune tolerance to HERVs should have been established. Contrarily, HERVs still show the capacity to evoke innate and adaptive immunity, and this is thought to occur mostly by molecular mimicry between common auto-antigens and, again, exogenous retroviral proteins, stimulating inflammation and auto-antibodies production [7]. In addition, HERVs can even act as super-antigens, eliciting an unspecific polyclonal activation of auto-reactive T lymphocytes and prompting massive cytokine releases [9]. Hence, HERVs are able to exert multifaceted effects on the host immunity, which go far beyond the mere concept of friends or foes, being the product of a complex and subtle interplay that evolves since millions of years, still long before human appearance. With regards to this, HERVs are known to have acted as major contributors in the evolution and shaping of the interferon response, being one of the most important pathways of innate immunity [10]. Particularly, different ERVs have independently expanded the interferon regulatory network in diverse mammalian lineages, disseminating a number of interferon-inducible genes that have been occasionally co-opted for the host immune control [10]. Thus, the elucidation of HERVs actual roles in influencing human immunity is just at the beginning, representing a wide panorama in which evolution, genetics, virology and immunology get overlapped in determining either the safeness or the damage of the host.

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