Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Virology

The biological significance of bornavirus-derived genes in mammals

Masayuki Horie[1,2]

The discoveries of sequences derived from non-retroviral viruses in eukaryotic genomes have significantly expanded our knowledge about virus evolution as well as the co-evolution between viruses and eukaryotes. However, the biological functions of such sequences in the host are largely unknown. Endogenous bornavirus-like elements (EBLs) have been relatively well studied by molecular biological methods, which have provided evidence that some EBLs have been co-opted by their hosts. This review highlights the current knowledge on the biological significance of EBLs, and discusses possible functions of EBLs. Further, we highlight the importance of extensive surveillance of exogenous viruses for a better understanding of endogenous viral sequences as well as the co-evolution of viruses and eukaryotes.

Addresses
[1] Hakubi Center for Advanced Research, Kyoto University, Kyoto, Japan
[2] Laboratory of RNA viruses, Department of Virus Research, Institute for Frontier Life and Medical Sciences, Kyoto University, Kyoto, Japan

Corresponding author: Horie, Masayuki (horie.masayuki.3m@kyoto-u.ac.jp)

Current Opinion in Virology 2017, **25**:1–6

This review comes from a themed issue on **Paleovirology**

Edited by **Aris Katzourakis**

For a complete overview see the Issue and the Editorial

Available online 27th June 2017

http://dx.doi.org/10.1016/j.coviro.2017.06.004

Introduction

Endogenous viral sequences (EVEs) are heritable sequences originated from viral nucleotide sequences in eukaryotic genomes [1]. The existence of EVE became apparent from a series of studies on retroviruses in the late 1960s to early 1970s [2]. Because retroviruses replicate via integration of their genomes into host chromosomes, they are endogenized, and once the viruses infect the host germ-line cells, they are inherited in a Mendelian fashion [2,3]. Endogenous retroviruses (ERVs) have a long history of study, which has provided us with important knowledge about paleovirology as well as the co-evolution between retroviruses and their hosts [2,3]. Interestingly, some ERV-derived genes have been co-opted by the hosts and have essential roles such as in placentation in mammals [4–7].

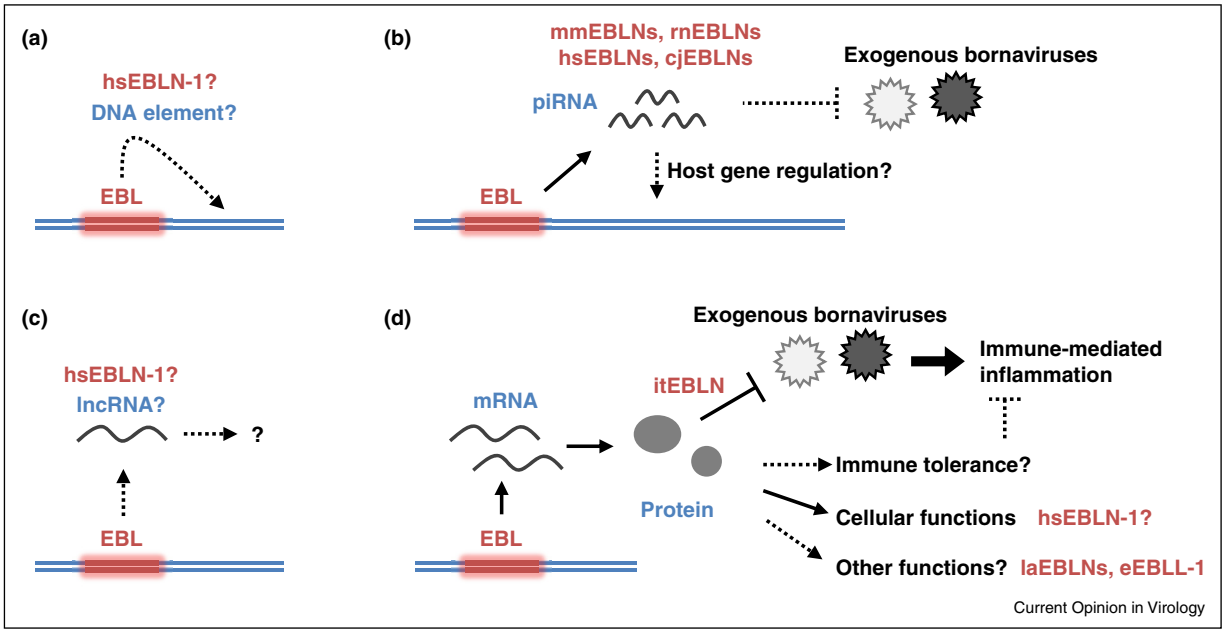
Although chromosomal integration is not essential for the replication of other types of viruses (DNA, RNA and DNA reverse-transcribing viruses), recent studies have revealed the presence of non-retroviral EVEs in eukaryote genomes [1,8–26]. Although studies of non-retroviral EVEs have provided interesting insights into the evolution of viruses as well as the co-evolution between viruses and their hosts, the biological significance of non-retroviral EVEs in their hosts remains largely unknown. Among the non-retroviral EVEs, bornavirus-derived EVEs, named endogenous bornavirus-like elements (EBLs), have been relatively well studied and have provided clues on the biological significance of non-retroviral EVEs in mammals.

Bornavirus-derived genes in mammals

Bornaviruses are non-segmented negative-strand RNA viruses belonging to the family *Bornaviridae* of the order *Mononegavirales* [27], which infect reptile [28], avian [29,30] and mammalian [31,32] hosts (summarized in [27]). Some bornaviruses cause fatal immune-mediated inflammation of the nervous systems [33,34]. Although bornaviruses are non-retroviral RNA viruses, bornavirus-derived sequences are widely distributed in vertebrate genomes, including human [1,8–10,35]. Bornaviruses harbor 6 genes encoding nucleoprotein (N), phosphoprotein (P), matrix protein (M), glycoprotein (G), RNA-dependent RNA polymerase (L), and accessory protein (X) [36••]. EBLs derived from the N, M, G, and L genes, which were designated as EBLN, EBLM, EBLG, and EBLL, respectively, have been reported [1,8–10]. Studies of the EBLs have given insights into the ancient bornaviruses; for example, the history of bornaviruses could be dated back to approximately 83.3 million years ago (MYA) [37••]. Additionally, some animal species that had not been identified as hosts of modern bornaviruses were found to harbor EBLs in their genomes, suggesting that the host range of bornaviruses is much wider than expected.

Additionally, EBLs have illuminated the evolutionary connections among the host genomes, retrotransposons, and virus infections [8]. Because bornaviruses do not carry the machineries for reverse-transcription and integration into host cells, the integration events have been suggested to be mediated by host retrotransposon machineries as in the case of cellular pseudogenes [8,10]. Indeed, the hallmarks of retrotranspositions are observed in some EBLs, such as poly-A tails and tandem repeat sequences flanking

Figure 1



Identified and speculated functions of bornavirus-derived genes. The identified (solid thin arrows and lines) and speculated functions (dashed arrows and lines) of EBLs are summarized schematically. EBLs involved in these functions are indicated in red. **(a)** EBLs might function as DNA elements such as promoters, enhancers, among others. **(b)** EBLs give rise to piRNAs, which might be involved in host gene regulation or antiviral defense. **(c)** Functional long non-coding RNA (lncRNA) might be transcribed from EBL loci. **(d)** EBLs encode functional proteins, which suppress the replication of exogenous bornaviruses or are involved in cellular functions, or which may give rise to immune tolerance to immune-mediated inflammatory diseases caused by bornaviruses or other functions. mmEBLN, *Mus musculus* EBLN; cjEBLN, *Callithrix jacchus* EBLN; rnEBLN, *Rattus norvegicus* EBLN.

the integrants, the so-called target-site duplications [8,10,37••,38•]. Additionally, a series of experiments revealed that the mRNA of a modern bornavirus integrates into the host cell chromosome with the characteristics described above [8], although the integration efficiency was very low [9]. Thus, EBLs have been formed through a combination of virus infections, host genomes, and retrotransposons.

EBLs are the only non-retroviral EVEs existing in the human genome and initial studies revealed the presence of transcripts from EBL loci in cell cultures and public databases [1,8,10]. Consequently, EBLs have been the subject of many studies, which showed the evidences that some EBLs have been co-opted by the host species (Figure 1).

Possible anti-bornaviral genes derived from ancient bornaviruses

Some ERV-derived genes have been reported to function as anti-viral genes against genetically similar viruses [39–42]. Theoretically, gene products from EBLs can also suppress bornavirus infections by the following mechanisms [9,43]. First, because a proper ratio of N to P proteins is required for optimal bornaviral replication, expression of N-like proteins in the host cell may disturb this ratio, resulting in the inhibition of viral replication. Second, if EBLs are relatively close to exogenous viruses or are derived from truncated viral genes, the gene products may act as dominant-negative proteins on exogenous viruses. Third, fatal diseases caused by bornaviruses comprise mainly immune-mediated inflammation. Thus, expression of EBL-derived proteins may lead to immune tolerance in the host (Figure 1d). This hypothetical mechanism cannot inhibit virus infection, but can suppress the development of symptoms caused by bornaviruses, conferring survival advantage to the host. Fourth, EBLN-derived non-coding RNA, such as small RNA, might suppress viral replication. Fifth, EBLs or their products might enhance or modulate the existing immune systems in the host [38•,43]. This section focuses on identified and speculated anti-bornaviral functions of EBLs in mammals.

An EBLN element in the thirteen-lined ground squirrel (*Ictidomys tridecemlineatus*) (itEBLN) is genetically very close to modern bornaviruses [8,44]. The endogenization of itEBLN was estimated to have occurred ~0.3 MYA [44], and the deduced amino acid sequence of itEBLN shows ~77% identity with the N proteins of modern bornaviruses [8,45••]. Additionally, at least in the squirrel heart, expression of itEBLN-derived protein was experimentally demonstrated [45••]. Because some ERVs were