Review

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Review

Mycobacterium paratuberculosis: A HERV Turn-on for Autoimmunity, Neurodegeneration, and Cancer?

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Abstract: Human endogenous retroviruses (HERV) are remnants of ancient retroviral infections that, over millions of years, became integrated into the human genome. While normally inactive, environmental stimuli such as infections have contributed to the transcriptional reactivation of HERV promoting pathological conditions including the development of autoimmunity, neurodegenerative disease and cancer. What infections then trigger HERV activation? *Mycobacterium avium* subspecies *paratuberculosis* (MAP) is a pluripotent driver of human disease. Aside from granulomatous diseases Crohn's, sarcoidosis and Blau syndrome, MAP is associated with autoimmune disease: type one diabetes (T1D), multiple sclerosis (MS), rheumatoid arthritis and autoimmune thyroiditis. MAP is also associated with Parkinson's disease. Autoimmune diabetes, multiple sclerosis and rheumatoid arthritis are the diseases with the strongest MAP/HERV association. There are several other diseases associated with HERV activation including diseases whose epidemiology and/or pathology would prompt speculation for a causal role of MAP. These include non-solar uveal melanoma, colon cancer, glioblastoma and amyotrophic lateral sclerosis (ALS). This article further points to MAP infection as a contributor to autoimmunity, neurodegenerative disease and cancer via unsilencing of HERV. We examine the link between the ever-increasing number of MAP- associated diseases, the MAP/HERV intersection with these diverse medical conditions and propose treatment opportunities based upon this association.

Keywords: *Mycobacterium avium* ss. *paratuberculosis* (MAP); Human endogenous retrovirus; HERV; Type 1 Diabetes; Multiple Sclerosis; Rheumatoid Arthritis; Amyotrophic lateral sclerosis (ALS); Alzheimer's disease (AD); Parkinson's disease (PD); Glioblastoma; Bromoepiandrosterone (BEA); Temelimab; BNN27.

1. Introduction

This article reviews proviral elements that have been incorporated into the human genome and presents the contributory role that these proviral elements play in autoimmunity, neurodegeneration and cancer [1–3]. Moreover, it identifies the role that a mycobacterial infection may have as an activator of these endogenized viral remnants.

1.1. HERVs

Human genes encoding proteins make up only 1-2% of the human genome [4]. Elements of exogenous virus infection have been incorporated into animal genomes over millions of years and are represented in the human genome where greater than 8% is comprised by these viral remnants [5,6]. First described in 1970, the human endogenous retroviruses (HERV) were discovered to have originated through ancient retrovirus infection and then incorporated into the germline and passed down through generations via Mendelian inheritance [7–10]. Repeated independent retroviral infections have generated unique HERV components leading to more than 100,000 HERV loci in

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humans [11]. While the number of inserted viral elements within the human genome is significant, complete proviral sequences are scarce. Through evolutionary processes involving recombination, deletion, and constant mutational events many HERV components have been removed from the host genome. As a result, most of these elements are incomplete or carry mutations that render them silenced and incapable of replication [12].

A notable exception involves two HERV proteins that are expressed fully in human pregnancy; these proteins have a role in human placental development as well specific tolerance to the semi allogenic fetal tissue to prevent rejection from the mother's immune system [13,14]. Needless to say, the conservation of "endogenized" retroviral genes that encode these functional proteins is important: the genes participated in evolutionary biology marking a transition from oviparity to viviparity [15].

HERVs have genetic structure analogous to that of exogenous retroviruses. They possess two long terminal repeats (LTRs) that enclose the internal coding sequence of the four fundamental retroviral coding domains: *gag*, *pro*, *pol*, and *env* that are exposed to the cellular milieu [16]. HERV nomenclature is somewhat arbitrary: HERV-K represents a group (frequently termed clade) of endogenous retroviruses that utilize lysine transfer RNA for their replication and integration into the genome [17]. Representatives of the HERV-K and HERV-W families are the primary focus of this review. The activation, or "unsilencing", of these genes can be promoted by infection[18]. An example of a microbial trigger of HERV activation is found in autoimmune diabetes (T1D): *Mycobacterium avium* subspecies *paratuberculosis* can activate HERV-W which plays a role in the etiopathology of T1D [19,20].

1.2. Mycobacterium avium Subspecies Paratuberculosis – MAP

Mycobacterium avium subspecies *paratuberculosis* (MAP), a unique zoonotic pathogen, poses a significant health risk at the intersection of animals, humans, and the environment [21]. It causes a fatal enteric infectious disease known as **Johne's disease** long studied in ruminant animals. Infected animals may not show clinical symptoms for years; yet, during this preclinical stage, the animals shed MAP in their milk and feces. This has led to a "don't test, don't tell" scenario in the industry, resulting in a higher prevalence of Johne's disease **[21]**. Moreover, pasteurization does not entirely eliminate MAP from contaminated milk, making it a source of exposure for humans; over 90% of dairy herds in the US have MAP-infected animals [22]. Milk and dairy products are the primary source of MAP infection in humans; pasteurization only partially reduces the MAP load originally present in milk, posing a consumption risk. MAP can also be found in yogurt, cheese, muscle meat, and hamburger [21]. The same bacterium, MAP, is the putative cause of Crohn's disease in humans. Countries that were historically free of Johne's disease acquired it through trade with infected animals, and Crohn's disease became a lagging indicator of MAP infection [21]. MAP is associated with an expanding list of human diseases several of which are delineated in this article. Besides Crohn's disease, the list included sarcoidosis, Blau syndrome, autoimmune diabetes, autoimmune thyroiditis, lupus, multiple sclerosis, rheumatoid arthritis and Parkinson disease [23].

2. Autoimmunity

When antigenic tolerance is lost to one's own self antigens the immune response is termed autoimmunity [24]. More than 100 autoimmune diseases have been described and they occur in up to 8% of the population with a higher prevalence in women [25]. Activation of the immune response by HERV can elicit uncontrolled inflammation that subsequently drives chronic inflammation contributing to the development of autoimmune diseases [26,27]. Mechanisms by which HERV can induce autoimmunity include 1) superantigens; HERVs can encode proteins that act as superantigens, particularly in CD4 T lymphocytes [28], 2) molecular mimicry; autoantigens from ancestral endogenous retroviruses once unsilenced, can have high homology with eukaryotic elements triggering an autoimmune response [29,30], 3) DNA hypomethylation; DNA hypomethylation is an epigenetic mechanism of DNA regulation, this is represented by the loss of

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the methyl group in the 5-methylcytosine nucleotide [31,32] and affects autoimmunity contributing to the pathogenesis of autoimmunity such as systemic lupus erythematosus [33,34].

2.1. Autoimmune Diabetes (T1D)

Type 1 Diabetes (T1D) is an autoimmune disease. The etiology of T1DM is incompletely understood but environmental agents are thought to trigger T1DM in the genetically at-risk. In the United States the prevalence of T1DM is increasing and is approximately 1 in 300 by 18 years of age. Research into risk factors for T1DM is an active area with attempts to identify genetic and environmental triggers that could potentially be targeted for intervention [35].

2.1.1. T1D and MAP

In 2006, Dow postulated that MAP may be an environmental trigger for T1D in the genetically at-risk. Three reasons led to the postulate: (1) shared genetic susceptibilities to both mycobacterial infection and T1D, (2) MAP is the source of the HSP65 protein, providing homology between mycobacterial HSP65 and pancreatic glutamic acid decarboxylase (GAD) and (3) consistent epidemiology findings tying the risk of T1D to early-life exposure to cow's milk [36,37]. Subsequently, Sechi and associates conducted several studies associating MAP and T1D. They found an association of MAP and T1D patients on their home island of Sardinia [38–40]. The island of Sardinia has the second highest incidence of T1D in the world [41]. They found MAP in T1D but not type 2 diabetics [42,43] and in children with T1D [44–46]. They confirmed shared genetic risk linking mycobacterial infection and T1D [47]. They also identified additional MAP peptides that are homologous with pancreatic proteins [40,46,48] and showed that immune reaction to these MAP peptides cross-react with classic islet cell antibodies [49]. Furthermore, they demonstrated parallel findings on the Italian mainland [50,51].

2.1.2. T1D and HERV

More recently in the same T1D demographic, Sechi leveraged the information that assorted environmental stimuli, including infection, may activate HERV to potentiate certain autoimmune diseases [52]. He and his associates demonstrated anti-HERV antibodies correlating with seroreactivity against MAP in children at risk for T1D. This study showed that an activated HERV gene expressing a specific envelope protein, HERV-W, is associated with T1D [20].

2.2. Multiple Sclerosis

Multiple sclerosis (MS) is an autoimmune demyelinating disease that involves the central nervous system and is characterized by infiltration of myelin-specific CD4+ T cells [53,54]. Identified host genetic risk factors for MS also increase the risk of susceptibility to mycobacterial infections. This includes polymorphisms of the major histocompatibility complex, TLR, vitamin D receptor genes, genes encoding IFN-gamma signaling components and SLC11A1 [55–57].

2.2.1. MS and MAP

MAP and MS are associated and this too was first studied on the island of Sardinia, where MAP is endemic [58]. The association has also been studied in Japan, where a seroprevalence study confirmed the association between MAP and MS [59]. Supporting the association of MAP and MS is the detection of MAP DNA in the peripheral blood of MS patients [60]. As with T1D, molecular mimicry is felt to play a triggering role in MS. Antibodies against MAP-specific protein MAP_2694295–303 and MAP pentapeptide (MAP_5p) are prevalent in the cerebral spinal fluid (CSF) and serum in those with MS. These peptides have homology with a component of myelin, the myelin basic protein (MBP). MBP is known as a prime target of autoimmune demyelination [61].

2.2.2. MS and HERV

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Several investigations provide strong indication of an association between MS and HERVs [62–66]. The presence of HERV-W immunoreactivity in active MS lesions is closely linked to areas of active demyelination throughout the progression of lesions in MS brains [67]. Antibodies against specific HERV peptide fragments have been identified in the serum and CSF of patients with MS; HERV-W env-su$_{93\text{-}108}$ and HERV-W env-su$_{248\text{-}262}$ [68] can distinguish those patients from those with other neurologic diseases.

2.3. Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune disease featuring pro-inflammatory cytokines that produce erosive joint damage and humoral and cellular immune responses against both self and infectious peptides [69].

2.3.1. RA and MAP

While the exact cause of RA is unknown, most agree that it is the result of complex interaction between host genetics and "environmental factors" [70]. The commonly cited infectious agents associated with RA are MAP and the Epstein-Barr virus (EBV) [71]. MAP and EBV are thought to secrete peptides that cross-react against RA-linked self peptides [69].

2.3.2. RA and HERV

HERV-K viral loads are elevated in RA patients compared to healthy controls; moreover, HERV-K is elevated in the synovial fluid of RA patients compared to patients with osteoarthritis [72]. The pathogenic mechanism of molecular mimicry linking HERV-K to RA has been advanced [73,74]. Specifically, HERV-K env-su$_{19\text{–}37}$ has high epitope homology with human antigens [75].

2.4. Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is considered a prototypic systemic autoimmune disease and is characterized by autoantibodies and multi-organ involvement [76].

2.4.1. SLE and MAP

The direct association of SLE and MAP is from a single case report [77]. The report shows that immunodominant mycobacterial heat shock protein 65 (HSP65) exuded by MAP shares homology with characteristic anti-Ro and anti-La autoimmune proteins associated with SLE.

2.4.2. SLE and HERV

While the association of MAP and SLE is nascent, the HERV/SLE association is well delineated. Numerous HERV sequences are indeed expressed at altered levels in SLE [78,79]. Both adult and pediatric SLE patients have IgG autoantibodies that recognize the envelope (Env) protein of HERV-K [80]. Immune complexes containing ERV-K102 envelope protein have the capacity to activate neutrophils which play a central role in the pathogenesis of SLE. When such complexes are cultured with neutrophils from healthy donors there is an induction of both neutrophil phagocytosis and neutrophil activation showing that HERV-K proteins are a target of SLE autoantibodies [81].

3. Neurodegeneration

Increasing epidemiologic and experimental data suggest a role for chronic bacterial and viral infections as risk factors for neurodegenerative diseases [82–84]. HERVs have repeatedly been implicated in brain disorders [85–87] and while this article will primarily discuss the age-related neurodegenerative diseases, it is worth noting the recognition of HERV in the etiopathology of schizophrenia [88,89]. Individuals with schizophrenia can be stratified into groups with differing inflammatory and clinical profiles based upon the presence of HERV-W antigens [90].

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Prion-like propagation of misfolded proteins is a hallmark of the age-related neurodegenerative diseases [91,92]. HERV un-silencing dramatically increases the dissemination of these protein aggregates, a process that can be inhibited by targeting the HERV protein [93].

3.1. Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS), also known as motor neuron disease (MND), is a progressively degenerative neurological condition that results in the loss of both upper and lower motor neurons located in the primary motor cortex and spinal cord [94,95]. This neuronal loss leads to muscle atrophy, ultimately causing the affected individual to lose control over bodily muscles and essential functions, such as respiration [95,96]. ALS is a highly intricate and diverse disease, characterized by variations in clinical symptoms and disease progression among patients [97]. This complexity makes diagnosing ALS challenging, often requiring patients to wait for up to a year from the onset of symptoms to receive a diagnosis. Currently, the underlying cause of ALS remains unknown, and there is no cure or therapy that can modify the course of the disease; the typical life expectancy for individuals diagnosed with ALS ranges from 2 to 5 years [98–100].

3.1.1. ALS and MAP

Reports of ALS clusters in professional rugby players, professional and amateur European soccer players and American football players led Pierce to propose MAP as a dirt-based infectious agent that can be introduced to athletes. The MAP exposure can come via inhalation of aerosolized pathogen, or after multiple oral, nasal or subcutaneous introduction of MAP present in the dirt, dust and grass of their playing fields [101]. Pierce et al. followed with a summary of two published case reports of ALS-like disease that responded to treatment with anti-mycobacterial antibiotics [102].

3.1.2. ALS and HERV

The transactive response DNA binding protein 43 kDa (TDP-43), which is typically located in the nucleus of neuronal and glial cells, plays a role in RNA regulation. In ALS, TDP-43 is mislocated and aggregated in the cytoplasm, leading to neurodegeneration [103]. The involvement of HERVs in ALS pathology is well recognized and is felt to occur through TDP-43 and neuroinflammatory mediators [104]. There are HERV-K transcripts found in the post-mortem brains of ALS patients [105]. Moreover, antibodies against a specific HERV peptide, HERV-K env-su$_{19\text{-}37}$, are elevated in both serum and CSF of patients with ALS and its presence can differentiate ALS from other neurogenerative diseases [68].

3.2. Alzheimer's Disease

Alzheimer's disease (AD) is the most common cause of dementia with a worldwide prevalence expecting to rise to greater than 60 million by 2030 and more than 150 million by 2050 [106]. The pathologic hallmarks of AD are extracellular amyloid plaques and intracellular tau tangles with these pathologies found up to 20 years prior to the onset of dementia [107,108].

3.2.1. AD and MAP

Although no specific agent has been identified as a cause of AD, a number of infectious agents have been linked to AD [84,109,110]. This association is bolstered by the knowledge that AD's primary pathologic protein, amyloid, is an antimicrobial peptide [111,112]. Mycobacteria in general [113] as well as MAP specifically [114] have been proposed as causal agents of AD. Gaining advantage due to heightened age-related immune risk, i.e., immunosenescence, infection by MAP may subvert cerebral glucose metabolism and exhaust autophagic capacity, both invariant features of AD and mycobacterial infection [113,115,116]. A number of anti-mycobacterial agents that suppress intracellular mycobacterial infection have been found to somewhat favorably impact AD; an epidemiologic study of leprosy patients treated with anti-mycobacterial drugs were found to have a significantly lower incidence of AD compared to those untreated [117]. Noteworthy is a proposed

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treatment of AD with the anti-mycobacterial drug, rifampin; intranasal delivery circumvents the known hepatic toxicity associated with clearance of systemic rifampin [118,119].

3.2.2. AD and HERV

HERVs have been implicated in the pathogenesis of AD [120,121]. Telescope is a tool that delineates HERV expression and is used to quantify this expression at specific genomic locations [122]. When applied in various datasets, this technology identified HERV-K differential overexpression in AD [123]. An interesting study of blood samples taken before and after individuals transitioned from normal cognition to AD showed what they described as a "storm" of differentially expressed transposable elements [124]. They postulated that this storm induces the immune-mediated neuroinflammation of AD and could be used as a biomarker heralding the phenoconversion from normal cognition to AD [124].

3.3. Parkinson's Disease

Parkinson's disease (PD) is a common, progressive degenerative disease of the nervous system manifest clinically by motor symptoms. These symptoms present when the burden of the hallmark aggregated protein inclusion bodies, Lewy bodies, reaches an advanced state [125]. Three lines of research have led to a greatly improved understanding of PD: 1) pathologic staging of the pathology of PD by Braak [126,127], 2) the segregation of initiating PD stimuli to "body first" or "brain first" [128,129], and 3) the identification of polymorphisms of the LRRK2 and PARK genes associated with PD that are also associated with susceptibility to mycobacterial infection and Crohn's disease [130,131].

3.3.1. PD and MAP

PD is the one neurodegenerative disease in which MAP has been found to play a role; initially postulated by Dow [132] then found by Sechi [133]. The LRRK2 genetic connection to both PD and Crohn's disease [134–136] lends support to this association. Intestinal symptoms are known to precede PD diagnosis [137]. The body-first iteration of PD is, in actuality, gut-first as PD proteinopathy arises in the enteric nervous system and propagates to the brain via the vagus nerve [138,139]. Body-first PD is first seen in the brain within its dorsal motor nucleus of the vagus nerve [140,141] . The historically relevant surgery, truncal vagotomy, is associated with lower subsequent risk of PD [142]. Brain first PD is also a misnomer as the PD cerebral pathology comes to the brain via the olfactory nerve [143,144]. Cerebral MAP infection through the olfactory nerve is conceivable; aerosolized MAP may lead to neuro-infection in the same manner of neuro-infection by *Neisseria* have been demonstrated by olfactory delivery [132,145].

3.3.2. PD and HERV

Wallace et al. used computational biology methods, experimental factor ontology enrichment analysis, to test for associations between HERV-K and various diseases. They found that HERV-K sites were statistically enriched for expressions in PD. This is measured as false discovery rate (FDR) and they found the chance of observing a false positive association between HERV-K and PD is 1.8^{-9} – that is an FDR of 0.0000000018 [146].

4. Cancer

HERV have been associated with a host of cancers [147–149]. This includes the hematologic cancers leukemia and multiple myeloma [150]. The diseases featured in the remainder of this section stem from the work of pathologist Ellen Pierce who coupled facets of MAP epidemiology as well as pathologic features to each of the maladies; in each section a discussion of MAP epidemiology as it relates to the oncologic malady and HERV follows.

4.1. Uveal Melanoma

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Cutaneous melanoma is the most lethal form of skin cancer; if detected and surgically treated early, survival rate is high. After metastasis, survival rates drop significantly [151]. Melanomas arising from the uveal layer in the posterior of the eye are distinct from cutaneous melanomas; while both arise from melanocytes, ultraviolet radiation that triggers cutaneous lesions does have not an equally predominant role in uveal melanomas [152]. Uveal melanomas do not have the molecular changes of cutaneous melanomas – changes that are attributable to ultraviolet exposure [153].

4.1.1. Uveal Melanoma and MAP

While there is no direct evidence of MAP and uveal melanoma, Pierce et al. note the high association of uveal melanoma with farming-related agricultural occupations [154]. They identify MAP-contaminated farm environment as a source of MAP exposure [154] where MAP persists in the farm soil, dust and water [155]. Farmers have an increased risk of developing uveal melanoma [156,157]. Pierce et al. describes a report of three clusters or "geospatial accumulations" of uveal melanoma and ascribes environmental MAP exposure to these clusters. They further posit MAP infection and resultant inflammation as a mechanism of cancer induction [158]. They describe the microenvironment of uveal melanoma as an inflammatory phenotype that prevents an efficient antitumor response[159]. They relate the estimated 80-90% exogenous environment factors associated with cancer and note the "hit and run" manner in which prior infections can trigger cancer [160].

4.1.2. Uveal Melanoma and HERV

A role for HERVs in melanoma is identified [161]. Mechanistically, HERV-D expression mediates intracellular fusion of melanoma cells that may drive the genetic changes that promote tumor growth [162]. The HERV association with melanoma appears to extend to both cutaneous and ocular melanoma as reported that a peptide from HERV is detected in both cutaneous and uveal melanoma tissues but not normal tissues [163].

4.2. Colon cancer

In 2020, Colorectal cancer was the third most common cancer and second leading cause of cancer deaths worldwide [164]. The inflammatory bowel diseases Crohn's and ulcerative colitis are associated with colon cancer [165,166]. Crohn's disease has long been associated with MAP [167] and there is also a MAP association, but less so, with ulcerative colitis [168].

4.2.1. Colon Cancer and MAP

MAP organisms have been identified in the intestines of patients with sporadic colorectal cancer where high magnification, oil immersion light microscopy was used (×1000 total magnification rather than the usual ×400 total magnification) [169]. MAP can cause acute and chronic intestinal goblet cell hyperplasia, an early pathologic feature of sporadic colon cancer leading Pierce to suggest that the persistent presence of MAP may result in, not only inflammatory bowel diseases, but also colon cancer [170].

4.2.2. Colon Cancer and HERV

There are several unique HERV-H loci expressed in colorectal cancer samples both from pathologic tissues and from cell lines [171,172]. The presence of the products of these specific HERV-related genes found in peripheral blood samples suggests a utility of their use as tumor biomarkers for these patients [173].

4.3. Glioblastoma

Glioblastoma is the most common primary brain tumor of adults; even with aggressive treatment median survival is only 15 months [174]. Infectious agents have been proposed as causes of nervous system cancers; this includes viruses [175,176] and the parasite *Toxoplasma gondii [177];*

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there have been two case reports relating *Toxoplasma gondii* to glioblastoma [178,179]. There is a notably increased rate of gliomas in rural residents who live in areas with domestic livestock [180–183]. While pesticide use was a suspected, it was dismissed in favor of a proposed zoonotic microorganism as the responsible agent for the increased rate in farm residents and workers [184,185]. Interestingly, there is increased rate of glioblastoma in tennis players, baseball pitchers and infielders as well as umpires [186]. Pierce suggests a pathologic equivalence between the pseudopalisading necrosis of gliomas and similar pathologic features of hypoxic mycobacterial granulomas [186,187].

4.3.1. Glioblastoma and MAP

An array of differentially expressed HERV elements are found in glioblastoma [188]. HML-2, a subtype of the HERV-K family, is expressed in a number of human cancers including glioblastoma [174,189]. The HERV-K overexpression is associated with glioma stem cells and an aggressive phenotype; also, down regulation of this expression with CRISPR results in decreased HERV transcription [190].

4.3.2. Glioblastoma and HERV

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5. Treating MAP/HERV

Recognizing a MAP/HERV association may open therapeutic pathways to treatment. Discussed here only in passing is anti-mycobacterial antibiotic treatments that are being used in Crohn's disease [191]. Rather what is presented is anti-viral treatment for HERV-associated disease as well as the potential of "upstream" treatment of the steroid metabolome and how that may favorably affect both MAP infection and HERV-associated disease.

An antiviral against HERV, GNbAC1 (now called Temelimab), is interestingly registered in clinical trials for both multiple sclerosis (NCT02782858, NCT01639300, NCT03239860, NCT04480307) [192] and autoimmune diabetes (NCT03179423); these are the two diseases with the greatest MAP/HERV association (as discussed in the autoimmunity section). Temelimab is an IgG4 monoclonal antibody that has been developed to specifically target HERV-W-Env and to neutralize the effect of HERV-W-Env, this therapeutic effort extends to HERV-W related cancers [193].

Both drugs and vaccines may find increasing utility in treatment of these diseases [148]. Anti-viral drugs are proposed in the neurodegenerative proteinopathies [93]. Anti-HIV retroviral drugs have demonstrated some benefit in ALS and they decrease HERV-K load after 24 weeks of therapy [194]. A strategy to augment tumor antigenicity via HERV-induced inflammation is another approach to fight cancer [149] including gliomas [195]. Moreover, it has been suggested that various tumors will be responsive to vaccines against HERV-K Gag [196]. Thus, HERV-targeting agents could provide a broad new class of therapeutics for autoimmunity, neurodegeneration and cancer.

An "upstream" approach to treat both mycobacterial infection and HERV-driven disease is proposed with an analog of dehydroepiandrosterone, DHEA. Levels of DHEA decrease and levels of cortisol increase with age and this ratio is associated with immunosenescence [197,198]. Direct DHEA supplementation is ineffective at one end of the spectrum and can cause serious side effects at the other end [199,200].

BNN27 is a new DHEA derivative absent unwanted steroidogenic effects; this agent has shown promise in animal studies [201]. HE2000, a synthetic analog of DHEA, found utility in the pre-antiviral drug era of HIV/AIDS [202]. It is a non-androgenic, non-anabolic steroid also known as BEA (16-bromoepiandrosterone). By acting to restore homeostasis to dysregulated metabolic/immune

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signaling networks BEA may provide a more youthful metabolome and immune phenotype [203] as demonstrated with an improved response to tuberculosis infection [204–207].

Cortisol may trigger HERV-associated diseases [208,209]; thus, efforts to develop a DHEA analog to increase the DHEA/cortisol ratio reminiscent of youth may alleviate many of the diseases presented in this article by restoring immune and metabolic homeostasis.

6. Summary

By any account MAP has been a formidable adversary for animal agriculture and animal and human health. Known for more than a century as the cause of Johne's disease, this fatal infection has continued to expand around the globe [21,22,210]. MAP has insidiously spread among animals and to humans by way of food, water, dirt and air. MAP can participate in the granuloma of granulomatous diseases and trigger autoimmune diseases by providing homologous epitopes to human self proteins. This article proposes another means by which MAP causes disease: the MAP initiated activation of long dormant viral elements – HERV – carried in our DNA which, when reawakened, transcribe proteins that look like us.

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