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Short Communication

Connecting Lupus and viral epigenetic hypomethylation

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Systemic lupus erythematosus (SLE) is an autoimmune disease with generation of autoantibodies attacking nuclear components and double-stranded DNA [1-4]. Normal cell turnover is programmed cell death and includes apoptosis-induced cell death with no internal cellular content spillover into the periphery. Improper cell death eludes this vital step of apoptosis-induced cell death and occurs with internal cellular content spillover exposing the focal immune cells to the nuclear and DNA debris, causing a reaction from the immune cells, which should not be exposed to these nuclear/DNA components and loss of self-tolerance [5]. This is one of the cycles of pathogenesis of SLE from sun exposure to UVB rays setting off an SLE-episode of autoimmune attack and generation of autoimmune antibodies. Evidence is mounting of the involvement of epigenetic modifications via DNA hypomethylation in the pathogenesis of SLE [6].

DNA methylation occurs to silence and inactivate genes, whereas active genes allowing gene expression are hypomethylated hence taken out of gene silencing by removing the methyl group [1,2]. This commonly occurs after DNA synthesis at the promoter region and first exon sequence at CpG islands [1].

Active SLE patients were found to be hypomethylators of the T cell lymphocyte line of T cells known as CD4+ which include the T-helper cells and the T-reg cells the suppressors of autoimmunity [1,4].

Active SLE patients were found to be hypomethylators of the T cell lymphocyte line of T cells known as CD4+ which include the T-helper cells and the T-reg cells the suppressors of autoimmunity [1,4]. To examine this further and continue to address the hypomethylation pathogenic etiology in SLE, we need to also discuss HERV and hypomethylation of the HERV genes in SLE. Human Endogenous RetroVirus (HERV) are interspersed repetitive sequences known as long terminal repeats of methylated cytosines [1] at approximately 9% of the human genome believed to be from ancient exogenous retrovirus infections [7]. These long terminal repeats are generally not infectious nor functional, however several have been found to still possess transcriptional abilities meaning they encode proteins as endogenous retroviral transcripts. Seifarth., *et al*. explains "many HERVs appear to have been silenced by cellular mechanisms such as methylation [7].

Hypomethylation of HERV allows for up-regulation of its transcript; HERV gene overexpression [4].

Two subgroups of HERVs with unsilenced hypomethylated long terminal repeats, hence activity and expression, are correlated with disease expression and progression in SLE, and they are HERV-E and HERV-K [1].

HERV-K gene expression encodes retroviral enzymes with functional similarities to HIV and was found to be expressed in nonactive SLE patients on daily immunosuppressants, but not normal controls and not active SLE patients [7]. A detrimental relationship exists between HERV-K and Epstein Barr Virus (EBV) with resultant powerful overstimulation of the immune system via generation of a superantigen, "microbial proteins that overstimulate the immune system". EBV is part of the herpesvirus family and successfully infects 95% of the human population, usually first exposure as mono [8].

Vazquez points out there are epidemiological and experimental studies correlating increased EBV re- activation in chronic autoimmune diseases including SLE (among others) activating HERVs [9].

EBV has evolved to evade the immune system and hide as it hijacks the host genetic material for replication, but as it lays quiescent in memory B cells, they do express latent proteins on their surface. If the immune system fails to attack these latent infected B-cells then EBV-reactivation occurs with significant increase in

EBV total viral load and re-infection [10]. It is at this latent stage and expression of latent proteins that the infected memory B cells transactivate its HERV-K18 gene inducing the superantigen. This EBV-HERV-K superantigen activates pro-inflammatory NF-kB and up-regulates pro- inflammatory cytokine IL-6; toxic and unwelcomed in the cytokine storm already persistent in the SLE patient as discussed in "Dietary Support for Lupus Cytokine and Viral Underlying Inflammation" [8,11].

Pathogenicity of hypomethylated T cells in SLE is correlated with hypomethylation of T cell HERV-E [1].

Pathogenicity of hypomethylated T cells in SLE is correlated with hypomethylation of T cell HERV-E [1]. HERV-E gene expression was detected in active SLE patients on immunosuppresants, but not in nonactive SLE nor controls. The HERV-E measurable detection was demonstrated via hypomethylation of CD4+ T cells [1,4]. HERV-E is also expressed in UVB sun-exposed SLE patients [4].

"Ultraviolet radiation is a pathogenic factor in SLE. UVB inhibited global DNA methylation in lupus CD4+ T cells but not in normal CD4+ cells". Wu., *et al.* continues "UVB inhibited HERV-E long terminal repeat methylation and induced HERV-E mRNA expression only in SLE patients" and concludes "UVB exacerbates SLE to a certain extent by inducing expression of HERVs via inhibition of DNA methylation" [4].

The active SLE patients exposed to UVB sunlight demonstrated decreased DNA methylation where the UVB exposure inhibited methylation and induced hypomethylation yet another correlation of hypomethylation-induced SLE pathogenicity [3,4]. HERV-E in SLE also promoted overproduction of inflammatory cytokine IL-6 [4] known to be overexpressed in their aberrant cytokine disease state and correlate to induction of B cell autoantibody [12].

In addition to the long terminal repeat (LTR) hypomethylation of CD4+ T cell HERV genes and their allowed concomitant expression and pathogenicity, SLE patient T cell autoreactivity was found to be due in part from hypomethylation of promoter sequences of T cell perforin and CD70 adhesion molecules, where this epigenetic overexpression exacerbated autoimmunity. The latter is also a part of the human genome interspersed repetitive sequences, but are non-LTR, also normally silenced with methylation.

This non-LTR is a retroelement called LINE (long interspersed nuclear elements) and in SLE is hypomethylated in both CD4+ and CD8+ T cell populations with subsequent autoreactivity [13].

Up-regulation and over-expression of LINE-1 and HERV result from hypomethylation [13].

With knowledge of the HERV pathogenicity in SLE and root cause from epigenetic hypomethylation, it's important to then address methylation support in the Lupus patient population in addition to avoidance of sun UVB exposure. The Methionine and Transulfuration pathways work together to maintain homeostatic levels of the universal methyl donor S-adenosyl-Methione (SAMe) and these pathways are largely dependent on the essential B-vitamins of B6, B9, and B12 as well as their essential mineral enzyme cofactors Zinc and Magnesium [14]. Genomic testing can also be conducted to evaluate polymorphisms (SNPs) affecting methylation necessary to coordinate efficiency of this cycle and are commonly seen in folate SNPs [15]. Anhydrous Betaine, also called TriMethylGlycine (TMG), is a good choice for a supplemental form and natural anti-viral support is recommended to address and/or prevent reinfection of latent viral infections like EBV as a safety against HERV expression and superantigen production [9,11].

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