The potential role of human endogenous retrovirus HERV-K10 in the pathogenesis of rheumatoid arthritis via molecular mimicry and the effect of autoantigen citrullination on rheumatoid factor reactivity

Malgorzata Trela[1], Prof. Paul Nelson[1], Dr. Shantha Perera[1], Prof. Paul Rylance[2], Dr. Kesley Attridge[3]

Faculty of Science and Engineering, University of Wolverhampton, UK [1]. Department of Nephrology, Royal Wolverhampton NHS Trust, Wolverhampton, UK [2], Aston University, Birmingham, UK[3].

INTRODUCTION

• Rheumatoid arthritis (RA) is a chronic autoimmune condition, that mainly affects the joints and is characterised by the presence of Rheumatoid Factor auto-antibodies (RF) to IgG1Fc and Anti-Citrullinated Protein Antibodies (ACPA) to citrullinated self-antigens such as fibrinogen.

• The expression of human endogenous retrovirus HERV-K10 is upregulated in RA patients thus it has been linked to RA as a potential trigger [1,2].

• HERVs, which constitute ~8% of our DNA, have been proposed as triggers of autoimmunity through molecular mimicry (similarity within fragments of amino acid sequence) between viral and host tissue proteins.

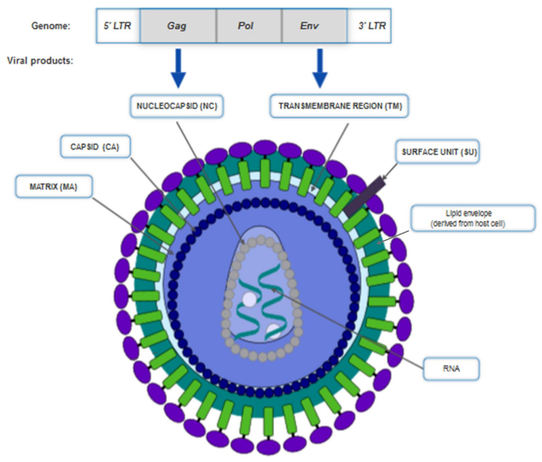


Figure 1. Schematic diagram of HERV showing Gag protein products.

• The Gag region of a HERV includes matrix, capsid and nucleocapsid proteins that protect viral RNA (Fig. 1).

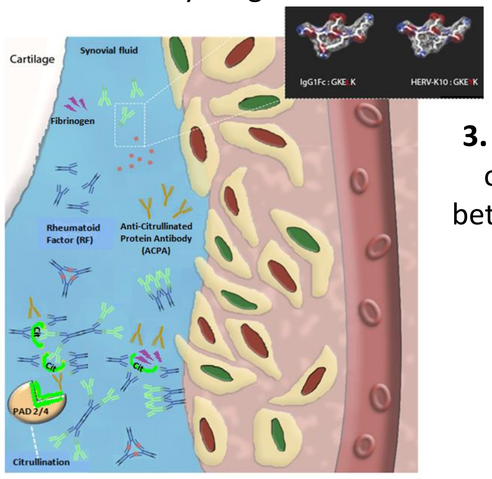
• Molecular mimicry between other HERVs and autoantigens has been observed in multiple sclerosis (HERV-W) [3] and lupus (HRES-1) [4].

• Post-translational citrullination of proteins in RA joints converts Arginine residues to Citrulline creating new targets for autoantibodies.

HERV-K10 AS A RHEUMATOID ARTHRITIS TRIGGER?

1. In healthy individuals Rheumatoid Factor (RF) is of IgM isotype and low affinity thus binds weakly to IgG1Fc

2. HERV-K10 is a molecular mimic for IgG1 Fc, but is expressed at low levels in healthy controls



3. In RA HERV-K10 is overexpressed and better presented due to mutations and environmental factors

4. Overexpression and enhanced presentation of viral mimics lead to RF antibody class switching to IgG and affinity maturation, causing RA onset and perpetuation

5. Post-translational protein citrullination with PAD enzyme further enhances autoantibodies reactivity to viral and host antigens

RESULTS

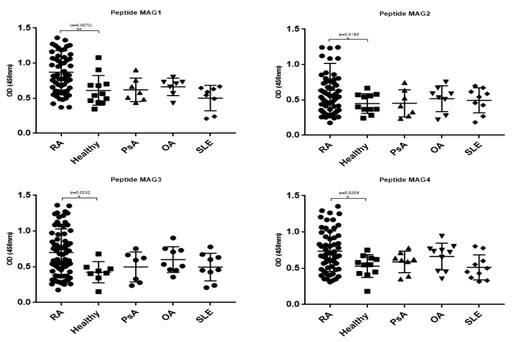


Figure 2. Serological response to four epitopes of HERV-K10 (MAG 1-4) in patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), osteoarthritis (OA), systemic lupus erythematosus (SLE) and healthy individuals.

• Significantly raised levels of antibodies to HERV-K10 in the sera of RA patients compared with rheumatological and non-rheumatological controls (Fig. 2).

• From bioinformatics, four regions of protein sequence similarity between HERV-K10 and IgG1Fc, likely to be targeted by antibodies.

• HERV-K10 peptide mimics confirmed to be structurally identical to IgG1Fc epitopes, even when amino acid substitution occurred (Fig. 3).

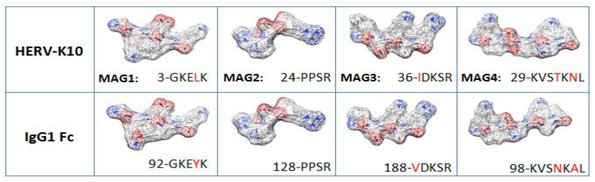


Figure 3. Structural and molecular mimicry between Rheumatoid Factor primary target IgG1Fc and K10 (MAG 1-4) viral peptides present in RA.

• Homology between native and citrullinated RA autoantigens, IgG1 Fc and fibrinogen (Fig.4).

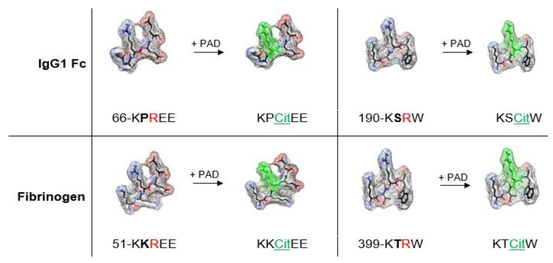


Figure 4. 3D structures of the regions of homology between IgG1 Fc and fibrinogen autoantigens.

• Enhanced reactivity of RFs from RA serum to citrullinated IgG1 Fc and fibrinogen autoantigens, when compared to their unmodified forms, even in the absence of ACPAs (Fig. 5).

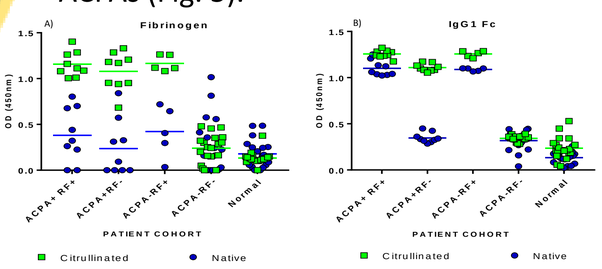


Figure 5. Reactivity of RF and ACPA autoantibodies from four RA patient cohorts to native and citrullinated forms of fibrinogen (A) and IgG1 Fc (B) autoantigens.

METHODS

We have investigated:

• The presence of antibodies to HERV-K10 Gag matrix viral peptides MAG1, MAG2, MAG3 and MAG4 in RA patient sera by ELISA.

• Molecular mimicry between HERV-K10 Gag matrix viral protein and IgG1Fc autoantigen using *in silico* analysis and molecular modelling.

• Conformational changes in autoantigen structure upon citrullination of the native protein

• The reactivity of serum from four RA patient cohorts (ACPA+RF+, ACPA+RF-, ACPA-RF+, ACPA-RF-) to native and in-house citrullinated forms of IgG1Fc and fibrinogen autoantigens.

SUMMARY

• Significantly increased levels of antibodies to HERV-K10 Gag viral matrix (MAG 1-4) are observed in rheumatoid arthritis.

• Molecular and structural similarity (mimicry) has been demonstrated between viral MAG epitopes and host IgG1 Fc regions.

• Protein citrullination appears to enhance Rheumatoid Factor autoantibody reactivity to host self-antigens even in the absence of Anti-Citrullinated Protein Antibody.

• Our findings could lead to development of blocking peptides or antibodies as novel therapeutic agents for RA.

1. Freimanis G., Hooley P., Ejtehadi H.D., Ali A.H., Veitch A., Rylance P.B., Alawi, A., Axford J., Nevill., Murray P.G., Nelson P.N. (2010) A role of human endogenous retrovirus (HML-2) in rheumatoid arthritis: investigating mechanisms of pathogenesis. *Clinical & Experimental Immunology.* 160, 340-347.
2. Trela M., Nelson P.N., Rylance P.B. (2016) The role of molecular mimicry and other factors in the association of Human Endogenous Retroviruses and autoimmunity. APMIS. 124, 88-104.
3. Do Olival G.S., Faria T.S., Nail L.H.S., de Oliveira A.C.P., Casseb J., Vidal J.E., Cavenaghi V.B., Tilbery C.P., Moraes L., Fink M.C.S., Sumita L.M., Perron H., Romano C.M. (2013) Genomic analysis of ERVWE2 locus in patients with multiple sclerosis: absence of genetic association but potential role of human endogenous retrovirus type W elements in molecular mimicry with myelin antigen. *Frontiers in microbiology.* 4, 1-7.
4. Perl A., Nagy G., Koncz A., Gergely P., Fernandez D., Doherty E., Telarico T., Bonilla E., Phillips P.E. (2008) Molecular mimicry and immunomodulation by the HRES-1 endogenous retrovirus in SLE. *Autoimmunity.* 41, 287-297.