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

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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.

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.

RESULTS

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.

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.

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

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 IgG1Fc, 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

SUMMARY

• 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).

• Homology between native and citrullinated RA autoantigens, IgG1Fc and fibrinogen (Fig. 4).

• Enhanced reactivity of RFs from RA serum to citrullinated IgG1Fc and fibrinogen autoantigens, when compared to their unmodified forms, even in the absence of ACPAs (Fig. 5).

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

REFERENCES


