

THE SILENT ENEMY WITHIN OUR DNA

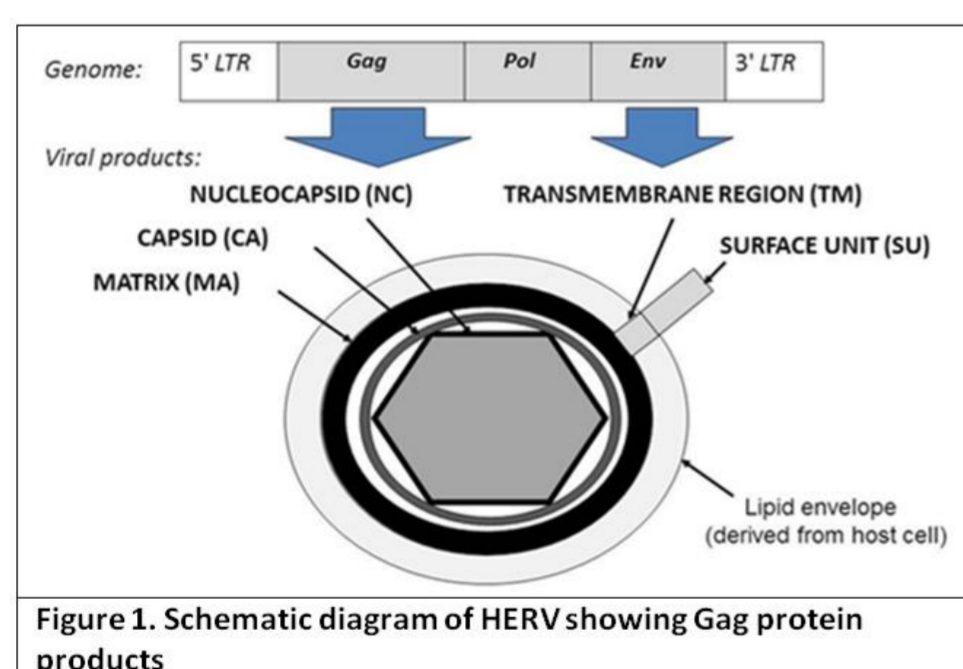
Human Endogenous Retrovirus HERV-K10 is a potential autoimmune trigger for Rheumatoid Arthritis through molecular mimicry

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Introduction

- Rheumatoid arthritis (RA) is a chronic autoimmune condition which involves the joints and causes destruction of cartilage and bone.
- Approximately 1-2% of the global adult population is affected by RA and the medical and social costs of this condition in the UK are £8 billion/year.
- Available RA therapies are limited by efficacy, side effects and cost.
- The aetiology of RA is likely a result of the interaction between genes, environment and viral agents.
- Human endogenous retrovirus HERV-K10 has been linked to RA as a potential trigger. HERVs constitute 8% of our DNA and represent ancient viral agents which have been passed through successive generations in a Mendelian manner.
- It has been proposed that they might trigger an autoimmune response through molecular mimicry (similarity within fragments of amino acid sequence) between viral and host tissue proteins. The Gag region of a HERV includes matrix, capsid and nucleocapsid proteins that protect viral RNA (Figure 1).



Methods

We have investigated:

- The presence of antibodies to HERV-K10 Gag matrix peptide GKELK (MAG1) in RA patients and compared it with control samples using ELISA system.
- Molecular mimicry between HERV-K10 Gag matrix protein and IgG1Fc (Rheumatoid Factor target) using bioinformatics and computer molecular modelling.
- The reactivity of a polyclonal antibody raised to viral peptide against serum IgG isolated from RA patients and IgG1Fc fragments using Western blotting and ELISA.

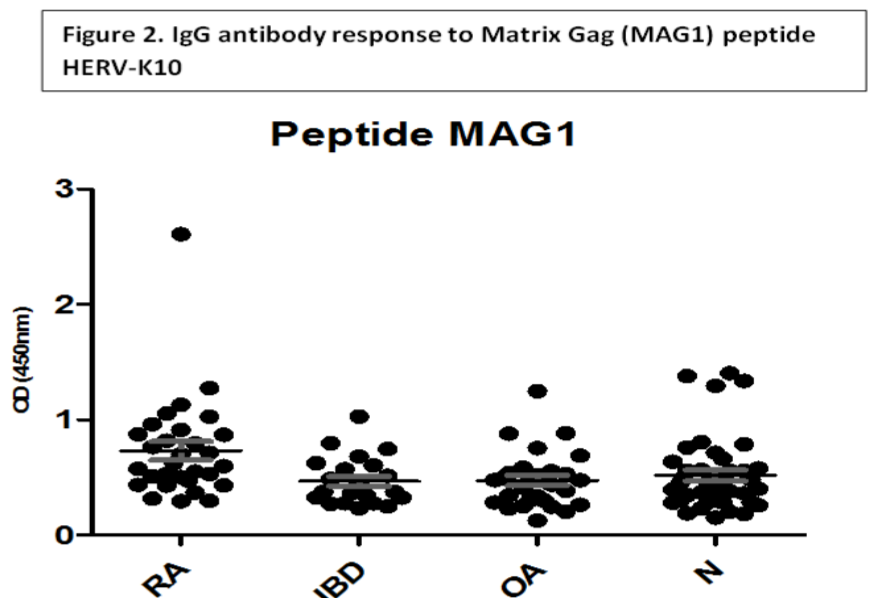
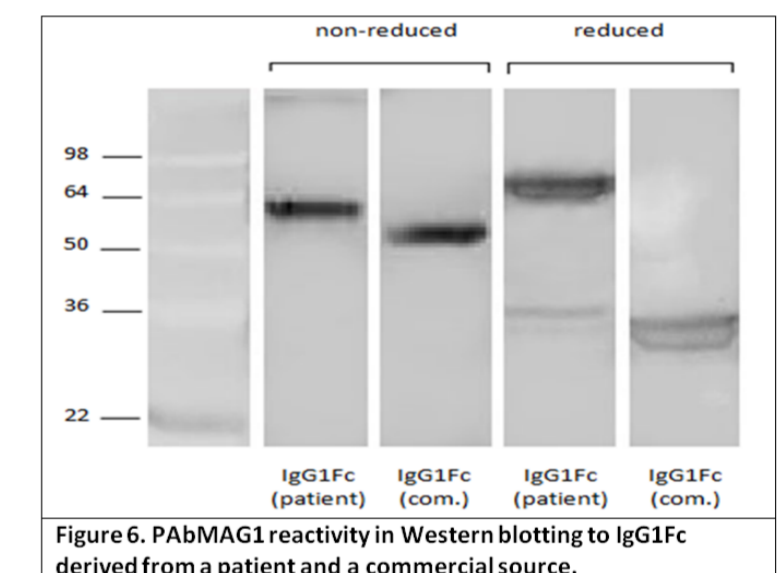
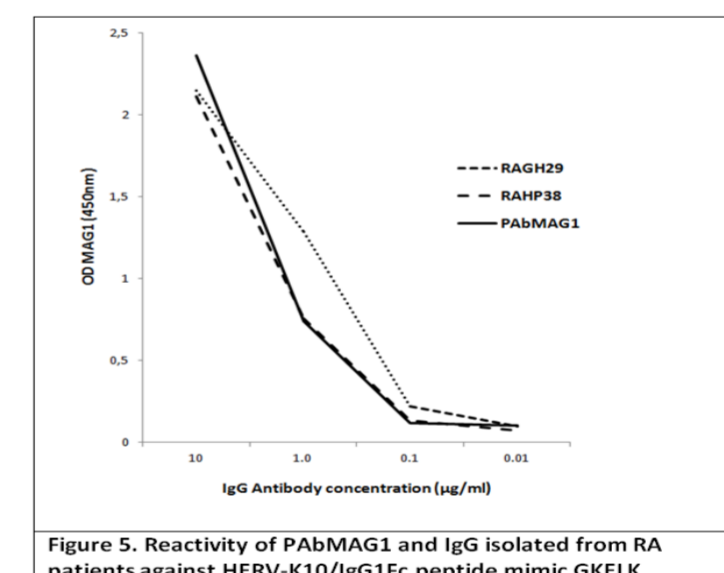
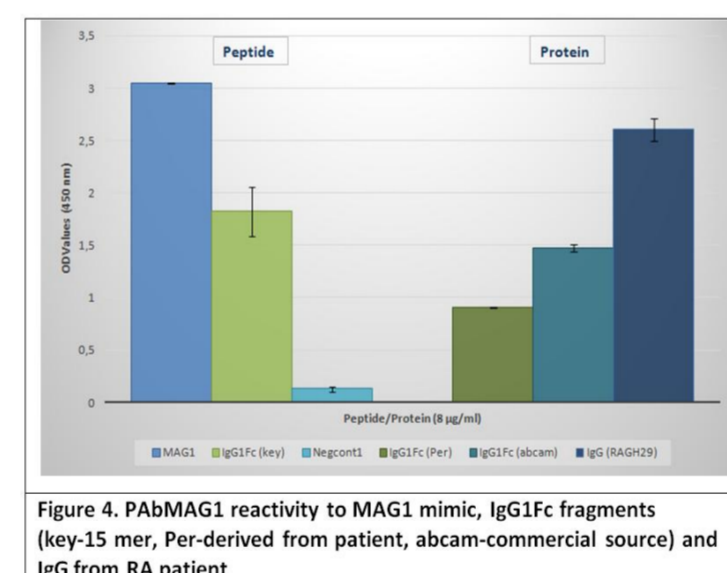
Results

Significantly raised levels of antibodies to HERV-K10 in the sera of RA patients compared with rheumatological and non-rheumatological controls ($p < 0.024$). (Figure 2)

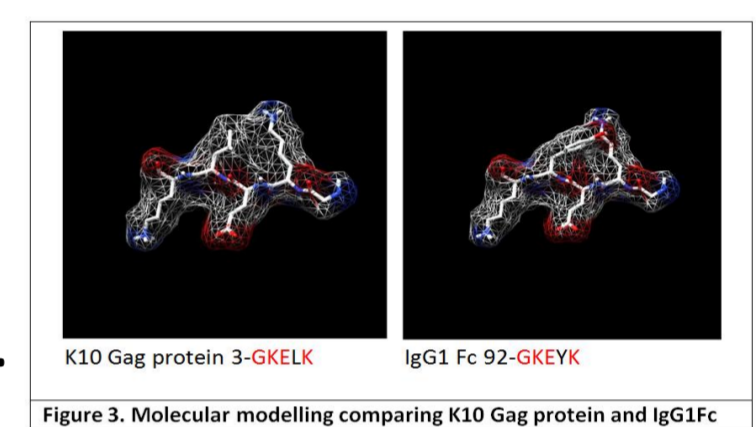
Six regions of protein sequence similarity between HERV-K10 MAG1 and IgG1Fc, likely to be targeted by antibodies (Table 1).

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

Antibodies specific for HERV-K10 Gag matrix peptide (PAbMAG1) bound to whole IgG and IgG1Fc fragments from different sources (Figure 4). Purified IgG from RA patients also detected the viral peptide mimic with equal titre to polyclonal antibody (Figure 5). Western blotting showed antibody reactivity to IgG1Fc (Figure 6).



HERV-K10:	GKELK	KVSTKNL	PELMG	PPSR	IDKSR	NGQP
IgG1Fc:	GKEYK	KVSNKAL	PELLG	PPSR	VDKSR	NGQP



Conclusions

- Significantly increased levels of antibodies to HERV-K10 Gag matrix are observed in RA.
- Molecular mimicry revealed between HERV-K10 MAG1 and IgG1Fc regions.
- The polyclonal antibody to MAG1 peptide (PAbMAG1) reacted with IgG1Fc. Purified antibodies from RA patients showed a similar titre to PAbMAG1.
- This finding could lead to development of blocking peptides or antibodies as novel therapeutic agents for RA.

References

- Tugnet, N., Rylance, P., Roden, D., Trela, M. and Nelson, P. (2013) Human endogenous retroviruses (HERVs) and autoimmune rheumatic disease: Is there a link? *Open Rheumatology Journal*. 7, 13-21.
- Nelson, P.N., Roden, D., Nevill, A., Freimanis, G.L., Trela, M., Ejtehadi, H.D., Bowman, S., Axford, J., Veitch, A.M., Tugnet, N. and Rylance, P.B. (2014) Rheumatoid arthritis is associated with IgG antibodies to human endogenous retrovirus Gag matrix: A potential pathogenic mechanism of disease? *The Journal of Rheumatology*. 41 (10), 1952-1960.