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A BLySful end to autoimmune disease?

Sharon Dorrell, Freelance writer

The discovery of a new member of the tumour necrosis factor family of proteins could lead to a new treatment for autoimmune diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA)[1]. The protein, B-lymphocyte stimulator (BLyS), which helps activate B lymphocytes and stimulate antibody production, is overactive in people with these diseases[2,3]. Human Genome Sciences (HGS) has applied to patent the protein and has developed monoclonal antibodies aimed at reducing abnormally high BLyS levels, and they are now being considered for clinical trials in patients with either SLE or RA. David Stump (HGS) anticipates that anti-BLyS antibodies will be given to patients for the first time later this year. The company is also looking at ways of using BLyS to boost immunity in immunocompromised individuals and a third avenue of research will investigate the use of radiolabelled BLyS as a dose titration or intermittent treatment for B-cell cancers.

BLyS

BLyS is a 285-amino acid membrane-bound protein expressed by monocytes, macrophages and other cells[1,2]. However, says Robert Kimberly (University of Alabama at Birmingham, AL, USA), a lead author of one of the recent studies of BLyS in patients with SLE (Ref. 3), it is not yet clear how the cells are activated to produce BLyS, although expression in monocytes is upregulated by interferon-γ[1].

BLyS binds to B cells and induces B-cell proliferation and antibody secretion (Fig. 1), but does not bind to T cells, natural killer (NK) cells or monocytes[1,2]. Transgenic mice that over-express BLyS display signs and symptoms similar to those seen in patients with SLE, including raised levels of antinuclear antibodies (ANA), anti-double-stranded DNA antibodies (anti-dsDNA), and rheumatoid factor, all of which support the link between BLyS and autoimmune rheumatological disorders[2]. Moreover, says Kimberly, 'Administration of a BLyS binding agent (either anti-BLyS antibody or a BLyS receptor protein) to transgenic mice helps ameliorate their autoimmune disease.'

Raised BLyS levels

SLE and RA are both chronic autoimmune disorders of unknown cause, although suggestions include inherited genes, environmental factors, joint damage and hormonal factors. While RA is characterized by stiff, painful and swollen joints, the problems associated with SLE range from skin rashes and joint problems to seizures and psychiatric problems. Treatment varies for RA but usually includes non-steroidal anti-inflammatory drugs (NSAIDs) to reduce joint swelling and pain. The current treatment for SLE largely depends on the severity of the illness and can range from NSAIDS or corticosteroids to immunosuppressive therapies.

Zhang and colleagues found that serum BLyS levels in 150 patients with SLE were more than twice the levels in 40 healthy volunteers[3]. There was no difference in the nature of the BLyS isolated from each group; it had the same molecular weight (17 kDa) and BLyS from

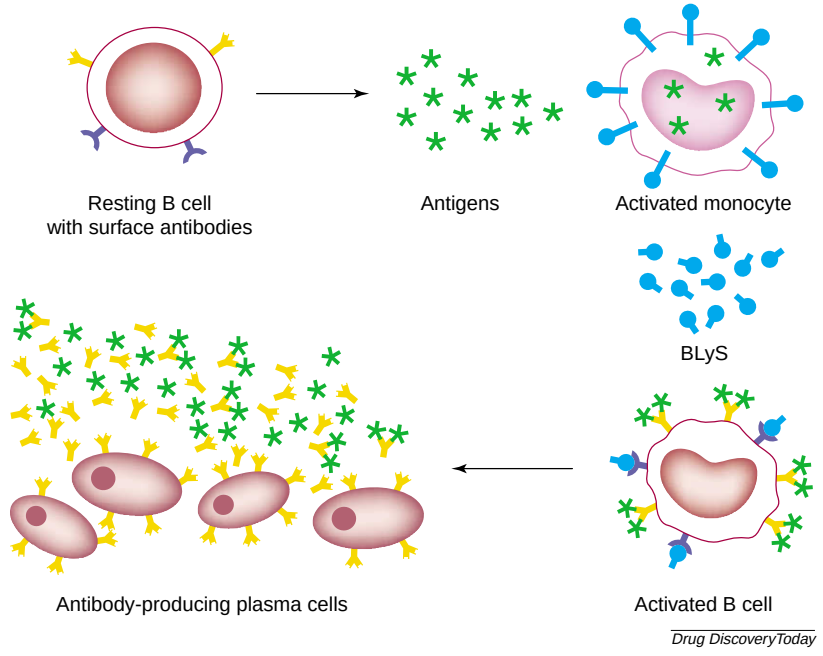

Figure 1. Mechanism of action of BLyS. Monocytes are activated by foreign antigens such as viruses and bacteria. These activated monocytes release BLyS which, together with foreign antigen, activate B cells. A primary consequence of this wave of cellular activation is the enhanced production of plasma cells (i.e. activated B cells), which will expand and produce more antibodies. [Reproduced with kind permission from Human Genome Sciences.]

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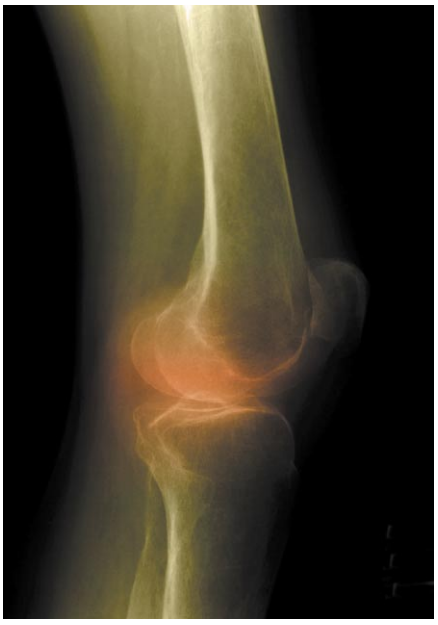
patients with SLE was fully functional and able to stimulate B cell activation *in vitro*. Raised BLyS was associated with a higher level of anti-dsDNA antibodies (a marker for SLE) but no increase in disease activity or damage. BLyS, the authors conclude, could therefore be a useful marker for autoimmune activation and probably also plays a crucial role in triggering activation of dsDNA-driven autoimmune B cells in people with SLE (Ref. 3).

A similar study measured BLyS levels in 22 patients with a variety of immune-based rheumatological disorders[2]. Cheema and coworkers found elevated BLyS levels in 15 patients and that these levels correlated with serum immunoglobulin levels.

Compromising immunity

Anti-BLyS antibodies will probably be administered as an intravenous or subcutaneous injection and could provide a therapy that patients self-administer once or twice a month. However, there is a chance that lowering BLyS levels could diminish B cell activity to such an



extent that patients become immunocompromised. However, Stump says, 'The BLyS receptor is not seen on early B-cell precursors. Therefore, if treatment is monitored carefully, this potential problem should be manageable by, for example, intermittent treatment to enable the stock of B cells to be restored.' Kimberly adds: 'Initial defence against viral infection is phagocyte-, NK cell- and T cell-mediated and so should not be impaired by these antibodies. Furthermore, endogenous antibody against tumours is not usually the first line of defence.' Kimberly concludes: 'In conditions where there is abnormally high B-cell activity (with antibody production), one can anticipate that reducing BLyS will be beneficial. However, as "normal" levels of BLyS seem very low, it is not yet clear what is required to maintain normal immune activity.'

References

1 Moore, P.A. *et al.* (2000) BLyS: member of the tumour necrosis factor family and B lymphocyte stimulator. *Science* 285, 260–263

2 Cheema, G.S. *et al.* (2000) Serum levels of B lymphocyte stimulator (BLyS) are elevated in patients with systemic immune-based rheumatological disorders. *64th Annual Meeting of the American College of Rheumatology*, Philadelphia, PA, USA, 29 October–2 November 2000, Abstract 165 (http://www.rheumatology.org/)

3 Zhang, J. *et al.* A role for B lymphocyte stimulator (BLyS) in systemic lupus erythematosus. *64th Annual Meeting of the American College of Rheumatology*, Philadelphia, PA, USA, 29 October–2 November 2000, Abstract 168 (http://www.rheumatology.org/)

Targeting 'good' cholesterol to treat heart disease

Anya Hillery, Freelance writer (also based at Department of Science, St Louis University, Madrid campus, Spain)

Current clinical strategies to manage blood cholesterol levels are confined solely to reducing the level of low-density lipoproteins (LDLs, or 'bad' cholesterol). However, scientists from CV Therapeutics (CVT, Palo Alto, CA, USA) have recently reported further advances on a mechanism to raise high-density lipoprotein (HDL, or 'good' cholesterol) levels[1]. Raising HDL levels offers an entirely new treatment solution for cholesterol management that could have a substantial impact on the prevention and treatment of cardiovascular (CV) disease.

Blood cholesterol and heart disease

CV disease is the largest single killer in the Western world. A high blood cholesterol level is a strong risk factor in CV disease because cholesterol can deposit on blood vessel walls, promoting the growth of fatty (atherosclerotic) plaques. These plaques obstruct blood flow and usually promote blood clotting, potentially resulting in, for example, myocardial infarction, stroke and peripheral vascular disease.

Cholesterol is transported in a soluble form in the blood as lipoproteins. LDLs deliver cholesterol to body cells that need it and high plasma LDL concentrations are associated with a high

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