other changes were observed, but this small change is consistent with the anti-inflammatory effects demonstrated during insulin infusion.

Glitazones

In a previous study, Dandona and colleagues demonstrated that troglitazone, one of the thiazolidinedione insulin sensitizer agents (also called the glitazones), reduced inflammatory activity in obese people[2]. They found that these changes were associated with vascular improvements consistent with those observed during long-term insulin therapy[3]. 'Thus, insulin and the insulin sensitizers exert an anti-inflammatory effect that, in the long term, may prove to be anti-atherogenic,' the researchers conclude.

Future clinical studies

Dandona and colleagues suggest future investigations into the inflammatory effects of insulin infusion therapy in patients with acute myocardial infarction. Such patients are known to benefit from insulin, say the researchers, possibly because insulin inhibits lipolysis and the production of prothrombotic free fatty acids. However, if free fatty acids also possess inflammatory activity, insulin might have another mechanism of action. Furthermore, this study also suggests that insulin therapy might play a greater role in the treatment of patients with type 2 diabetes, which is associated with a high risk of atherosclerosis and its complications.

References

1 Dandona, P. *et al.* (2001) Insulin inhibits intranuclear factor κB and stimulates IκB in mononuclear cells in obese subjects: evidence for an anti-inflammatory effect? *J. Clin. Endocrinol.* 86, 3257–3265

2 Garg, R. *et al.* (2000) Troglitazone reduces reactive oxygen species generation by leukocytes and lipid peroxidation and improves flow-mediated vasodilatation in obese subjects. *Hypertension* 36, 430–435

3 Vehkavaara, S. *et al.* (2000) Insulin therapy improves endothelial function in type 2 diabetes. *Arterioscler. Thromb. Vasc. Biol.* 20, 545–550

New antibody therapies for HIV

Martina Habeck, Freelance writer

Novel monoclonal antibody-based therapies for the treatment of HIV are currently being evaluated in the laboratory and, increasingly, in clinical trials. Tanox (Houston, TX, USA) has recently announced a Phase I clinical trial of a monoclonal antibody that works by binding to the CD4 receptor on the host-cell surface. Meanwhile, a team of researchers at Rockefeller University (New York, NY, USA) has just published new research[1] that could lead to an alternative antibody-based therapy that would prevent or reverse mechanisms of HIV pathogenicity attributed to the HIV Tat protein, a protein that would otherwise destroy CD4 cells and lead to the progression of HIV to AIDS.

Preventing viral entry

HIV-1 entry into the host cell requires the binding of glycoprotein 120 (gp120) to the CD4 receptor on the host-cell surface. This interaction triggers a conformational change in gp120 that exposes its co-receptor binding site. Once gp120 has attached itself to both the CD4 receptor and its co-receptor, membrane fusion becomes possible and the virus can enter the host cell.

The monoclonal antibody TNX-355 (formerly Hu5A8) interferes with this process by binding to the extracellular domain 2 of the CD4 receptor. This does not inhibit the initial attachment of the virus to the CD4 protein, because the virus binds to domain 1. However, it blocks the conformational change of gp120, thereby preventing viral entry into the host cell.

To assess whether a humanized form of the antibody would be an effective and well-tolerated treatment for HIV, researchers at Tanox and elsewhere have done extensive preclinical tests[2]. William Shanahan, Chief Medical Officer at Tanox says that their studies showed that the antibody is effective *in vitro* at blocking infection across a broad spectrum of isolates of all the major HIV-1 subtypes. Further studies suggest that TNX-355 is unlikely to be immunogenic in humans because it has a fully human IgG core and the Fab (fragment antigen-binding) region originates from a humanized murine antibody. Moreover, the antibody is unlikely to interfere with the immune function of CD4, because this function is mediated through domain 1 of the receptor, an assumption that was confirmed by *in vitro* studies in human and monkey blood cells. *In vitro* tests also showed no induction of blood-cell apoptosis, and there was no depletion of CD4 cells in monkeys.

The investigators hope that their treatment approach will circumvent drug resistance, because the target is a human glycoprotein rather than a highly mutable viral protein. The Phase I dose-escalation study that is about to start will evaluate the safety and tolerability of a

1359-6446/01/$ – see front matter PII: S1359-6446(01)02009-8

single intravenous infusion of the antibody in patients that have failed two courses of highly active antiretroviral therapy (HAART). If this Phase I study goes well Tanox plans to provide coverage for two months in the Phase II study.

Sandra Bridges at the Division of AIDS at the National Institute of Allergy and Infectious Diseases (Bethesda, MD, USA) says, 'If all goes well, this type of antibody might also be used in the preventive mode, that is, after occupational exposures such as needlestick injuries.'

Stimulating the innate immune system

Toby Rodman, Professor Emeritus at Weill Medical College of Cornell University (New York, NY, USA) has discovered innate IgM antibodies that are reactive with the HIV Tat protein and could restrict HIV pathogenicity. Rodman first identified the antibodies eight years ago when studying the chemistry of protamines. 'We found antibodies present in circulating human sera that were reactive with certain arginine-rich sequences on protamines. A database search revealed that the epitope for this sequence is also part of the Tat protein of HIV.' She has previously shown that these antibodies are present in humans of all ages, which characterizes them as innate. However, they appear to be species-specific, because they were also found in chimpanzees, but not in monkeys and rodents[3]. Rodman and colleagues have established that HIV-negative humans maintain a relatively constant level of these antibodies, but that different people have different levels. The antibodies are also present in HIV-positive humans, but their level decreases when they progress to AIDS[3]. By contrast, so-called long-term non-progressors maintain normal levels of the Tat-reactive antibodies.

It is, therefore, becoming increasingly clear that to develop an effective HIV vaccine, more needs to be known about the innate immune system. Rodman suggests that the human immune system might mistake the antibody-reactive sequences of Tat as self-antigens[3]. This could evoke tolerance, resulting in a broad deletion of B cells that secrete these innate antibodies, and hence, contributing to the state of extreme immunodeficiency in AIDS.

Most recently, Rodman and colleagues report that IgM pools isolated from the blood of humans or chimpanzees do indeed inhibit Tat-induced T-cell apoptosis[1], whereas no such effect was seen with IgM pools from rhesus macaques or mice. By using human cord-blood B cells, they have also prepared a hybridoma that secretes monoclonal IgM antibodies reactive to Tat protein sequences. This confirms that these antibodies are innate because they are already present in embryonic cells.

Rodman believes that her findings could one day lead to the development of a novel therapeutic agent that can replace the innate antibodies that appear to decline as disease progesses. However, Bridges cautions that it is early days to talk about therapeutics: 'I think it is an important observation that these antibodies are there, and the work presented in the paper is well controlled. However, from the therapeutic viewpoint, I would like to see some data from animal studies to confirm that this could actually make a difference *in vivo*.' She adds that IgM antibodies have a low affinity and specificity, which is why passive immunotherapy approaches generally use IgG antibodies.

References

1 Rodman, T.C. *et al.* (2001) Circulating natural IgM antibodies and their corresponding human cord-blood cell-derived MAbs specifically combat the Tat protein of HIV. *Exp. Hematol.* 29, 1004–1009

2 Reimann, K.A. *et al.* (1997) A humanized form of a CD4-specific monoclonal antibody exhibits decreased antigenicity and prolonged plasma half-life in rhesus monkeys while retaining its unique biological and antiviral properties. *AIDS Res. Hum. Retroviruses* 13, 933–943

3 Rodman, T.C. *et al.* (1999) The human uniqueness of HIV: innate immunity and the viral Tat protein. *Hum. Immunol.* 60, 631–639