science, it is very difficult to go forward,' he remarks. 'This is a fundamental discovery, and people find it hard to believe that such a discovery could not have been made much earlier.'

Indeed, his findings could have a major impact on the way we look at where cells come from and how embryos develop. 'We would have to go back and look at the contribution of VENT cells to every tissue of the body,' says Sohal.

Eventually, this research could shed light on the pathogenesis of congenital disorders, for example, ailments of the gastrointestinal tract. Take Hirschsprung's disease, a disorder that affects one in 5000 babies and that is characterized by the absence of the ENS in the hindgut. Don Newgreen at the University of Melbourne, Australia (http://www.unimelb.edu.au), suggests that, if there really are two pathways to arrive at the same cell type, and if the VENT cells really are a cell source that is of functional importance, it might be possible to use them to replace defective or absent ENS cells. Also, 'comparisons [between the two routes to ENS development] will help greatly in identifying the common pathways we could focus on and control, pharmacologically or by cell or gene therapy,' adds Newgreen. According to Sohal, cells originating from heterogeneous sources might also express different receptors and could thus require treatment with different drugs.

But these are all hypothetical applications. The immediate challenge for Sohal and colleagues is to isolate the VENT cells. 'Once we have a specific marker for these cells, and once we have identified genes that are uniquely expressed in these cells, more people will be convinced,' believes Sohal.

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Anticancer drug shows promise against lupus

Vida Foubister, freelance writer

A drug that is currently in Phase II clinical trials for use as an anti-tumour agent has been found to reduce the expression of cytokines that contribute to immunopathogenesis in lupus patients. Furthermore, a structurally related compound significantly reduced the clinical symptoms of lupus in a mouse model, including urine protein excretion, enlarged spleen and kidney disease. Scientists are optimistic that the anti-tumour drug could enter clinical trials for lupus within two years.

Histone deacetylase inhibitors

The two drugs, suberonylanilide hydroxamic acid (SAHA) and trichostatin A (TSA), belong to a class of compounds that alter the acetylation of histones [1,2]. Specifically, they act by inhibiting histone deacetylase and thus increase histone acetylation. Histones regulate the packaging of genes into chromatin; the acetylation and deacetylation of histones result in changes to the chromatin structure that ultimately affect gene expression.

TSA is a naturally occurring compound produced by *Streptomyces*. It was identified in 1974 and was subsequently found to inhibit histone deacetylase, said Nilamadhab Mishra, Instructor in Internal Medicine at Wake Forest University School of Medicine (http://www.wfubmc.edu/school/).

SAHA, a second-generation histone deacetylase inhibitor based on the structure of TSA, has entered Phase II clinical trials in cancer patients. Aton Pharma (http://www.atonpharma.com/) the sponsor of these trials, report that it has excellent oral bioavailability and long duration of action, and can inhibit histone deacetylase at well-tolerated doses.

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Neither of these drugs demonstrated toxicity in the recent lupus study [3]. Specifically, TSA and SAHA did not impact mouse splenocyte viability at effective concentrations and, in addition, TSA-treated mice showed no evidence of liver or lung toxicity. 'They ate well, they gained weight, they seemed healthy,' said Gary S. Gilkeson, Professor of Medicine at the Medical University of South Carolina (http://www.musc.edu/).

Unmet need for therapies

Systemic lupus erythematosus is an autoimmune disease that is a leading cause of morbidity and mortality in young black women. It is currently treated with high-dose chemotherapy – an approach that carries significant risks, including sterility. Patients receive repeated treatments over the course of two years, first with doses once a month and then once every three months.

'We are able to help [patients] have prolonged survival,' said Gilkeson. 'But when they don't die from the lupus, they are developing heart attacks and strokes in their 20s. Part of that is due to the therapies, the immunosuppression, and part of it is due to the disease.'

The MRL–*lpr/lpr* mice used in the recent study spontaneously develop a lupus-like disease [4]. They produce autoantibodies and develop the skin rash, arthritis, enlarged spleen and kidney disease that is seen in human lupus. However, the human disease is more complex and its outcome more variable than this mouse model represents. Lupus, for example, affects women nine times more than men, while female and male MRL–*lpr/lpr* mice are equally affected.

'What is wrong genetically in one mouse model might not match what is wrong genetically in human lupus,' explained Joan Merrill, Head of the Clinical Pharmacology Research Program at the Oklahoma Medical Research Foundation (http://www.omrf.org/). 'But it might point to one of the pathways that are aberrant in humans.'

Proof of concept

MRL–*lpr/lpr* mice, like human lupus patients, overexpress specific inflammatory proteins. An earlier study demonstrated that TSA can reverse aberrant cytokine expression in human systemic lupus erythematosus T cells [5].

Building on those results, researchers in the current study found that TSA and SAHA decreased the expression of IL-12, INF-γ, IL-6 and IL-10 in MRL–*lpr/lpr* splenocytes at both the messenger RNA and protein level. At the same time, these drugs increased the acetylation of histones H3 and H4. 'We think they are changing the chromatin structure and by that affecting gene expression,' Mishra said.

Their next step was to treat MRL–*lpr/lpr* mice with TSA. 'When we did that, the mice had less severe manifestations of disease,' said Gilkeson. Namely, there was a significant reduction of excess protein in the urine, as well as reduced spleen weight and kidney inflammation. Future studies will examine the effect of SAHA on the disease progression and long term survival of MRL–*lpr/lpr* mice and other mouse models of lupus, with the goal of entering clinical trials within two years.

Histone deacetylase inhibitors have a broad spectrum of action, however, and it is possible they will have too many side effects for therapeutic use. 'Basically all the drugs we have now globally suppress the immune system,' Merrill said. 'We're looking for drugs that target what's aberrant in lupus.'

Building on the cancer trials

Although there is a tremendous need for new lupus therapies, progress has been slow. Lupus is a complex disease without a large enough patient base to attract the attention of most pharmaceutical companies. 'The expenses are exorbitant in lupus trials, the outcomes are uncertain and the final product isn't going to be a blockbuster drug,' Merrill admitted.

Thus, SAHA is an attractive candidate for drug development as the cancer clinical trials will help to establish its safety and efficacy in humans. 'It will certainly help us to have some idea of what doses to start out with in humans and to know if there are any unforeseen side effects,' said Gilkeson.

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