Pretzel-shaped peptide for autoimmune disease

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By flipping a peptide upside down and inside out, an Ohio State University (http://medicine.osu.edu) researcher has created a molecule that appears to turn off a T-cell stimulant in autoimmune disease, while largely leaving the T-cell suppressor alone. The Director of Biomedical Research Services for the National Multiple Sclerosis Society (http://www.nmss.org), Patricia Olooney, calls it, 'the next stage of treatment for autoimmune disease.'

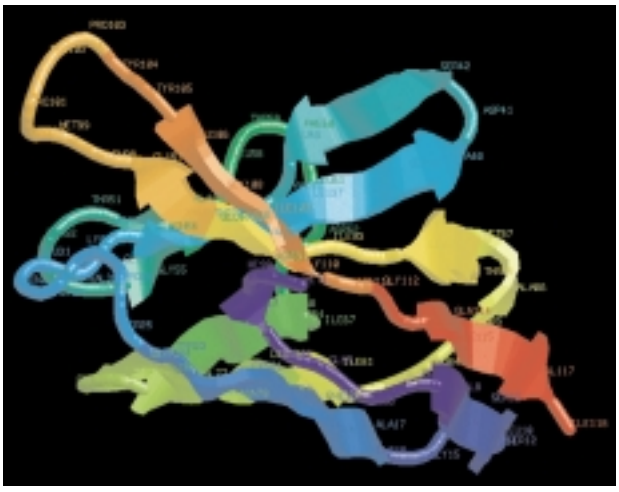

Figure 1. Pictured is a 3D model of the region of the CD28 receptor used to create the therapeutic peptide (model provided by Jurgen Bajorath, Albany Molecular Research). Image kindly provided by Pravin Kaumaya.

Unwanted T cells

The team at OSU has shown that the artificial immune-system peptide prevented and even reversed ongoing experimental autoimmune encephalitis (EAE), a mouse model of multiple sclerosis (MS) [1]. Although the researchers caution that the treatment might yet be shown to suppress the immune system globally, they are optimistic that it is truly selective. 'I think it could be useful anytime there are unwanted T cells,' says Caroline Whitacre, Chair of Molecular Virology, Immunology and Medical Genetics at the OSU's College of Medicine and Public Health, and lead author of the study. The treatment could enter clinical trials as soon as two or three years from now, according to its developers.

In MS (which affects 300,000 Americans, often in young adulthood) immune T cells attack the myelin sheath surrounding nerve cells in diffuse areas of the brain. This demyelination causes the neuron to 'leak,' so that it can no longer send signals to the brain or to muscles. The results are varied and unpredictable, from double vision and tingling sensations to muscle fatigue, and later, muscle spasms and pain, poor coordination, and eventually blindness or paralysis. At present, MS is managed either with β-interferon, which down-regulates the immune system, or with symptomatic remedies, such as corticosteroids to reduce the immune response, muscle relaxants to relieve spastic muscles, stimulants to reduce constant fatigue, and counseling (not surprisingly, depression often accompanies MS).

Olooney says that, 'While these treatments do a wonderful job, they are not the end of the story.' The path towards a solution to multiple sclerosis research is strewn with attempts to conquer EAE, with conflicting results [2–4]. Some tactics even worsened the course of the disease in human trials [5]. Olooney notes that the strength of the new peptide is its specificity for T cells, because it apparently blocks only the immune cells that cause the damage, rather than the entire system.

Stop and go signals

T-cell activation involves a dizzying array of signaling molecules, including the CD28 and cytotoxic T-lymphocyte antigen (CTLA) receptors on the T-cell surface, and their ligands, the B7 molecules [6]. When B7 binds at CD28, it acts as a 'go' signal for T-cell activation, but at the CTLA receptor it delivers negative feedback to the immune system. 'The innovation is that we can block the 'go' signal while leaving the 'stop' signal intact; it's a one-two punch against autoimmune disease,' explains Whitacre. The therapeutic peptide masquerades as the binding site of CD28, binds B7, and prevents an interaction between B7 and the genuine CD28. The negative-feedback receptor CTLA, however, binds B7 with about 20-times higher affinity than CD28, so that the peptide does not significantly interfere with the T cells' 'stop' signal.

Biochemist Pravin Kaumaya, designer of the synthetic peptide in the study, used the binding motif of the CD28 receptor as the foundation (Fig. 1). His challenge was to create a stable peptide, but Kaumaya notes, 'duplicating the native structure of the peptide is very important for ligand–receptor interaction.'

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The natural L-amino peptide has a relatively short half-life, whereas the D-peptide is safe from proteolysis. Kaumaya's challenge was to make a stable peptide while preserving the receptor structure. By creating a 'retro-inverso' molecule, in which the sequence is reversed and inverted, his laboratory made a stable peptide that is a perfect mirror image of the CD28 receptor's binding motif.

A question of specificity

Before entering human trials, Whitacre says the strategy must pass a crucial test in animals: does it act as a global immunosuppressant? 'If a person [treated with the redesigned peptide] meets a virus, can they still fight it off? We don't want to lay people open to infection.'

Another piece of data from the study might hint at the answer: in mice, treatments with the peptide mimic reduced the T-cell population through apoptosis. 'Now we need to go in and ask, which specific T cells are they? Is it a global lowering of all T-cells?' says Whitacre. By contrast, if it is only pathogenic-specific T cells that are affected, then Whitacre says 'that's very exciting. Then we're purging an MS patient of the specific disease-causing T cells.'

Although this study is an early step toward the development of a treatment for MS, the data in the EAE mouse model even hint that the peptide might actually reverse the course of MS, according to Whitacre. Further, because it acts at the source of the immune attack, it could also work in other problems involving the immune system, such as graft vs host disease or organ transplantation.

References

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Boost for retinoic acid cancer therapy

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A naturally occurring protein can dramatically enhance the ability of retinoic acid (RA), a common cancer therapy, to inhibit the proliferation of breast cancer cells. The finding may make it possible to fine-tune this drug's activity to avoid harmful side effects.

RA, a vitamin A derivative, is a small signalling molecule that plays an important role the regulation of cell growth, differentiation and death. Because of their ability to drive cells towards apoptosis, RA and other retinoids are used successfully in the treatment of acute promyelocytic leukemia. They also have potential to prevent cancers of the skin, head and neck, and lung.

Although the function of RA in regulating cell growth and differentiation has been known for a while, the molecular mechanisms by which these functions are regulated are still under investigation. Scientists know that RA binds to a family of nuclear transcription factors, the RA receptors (RARs), thereby inducing the transcription of target genes. RA can also bind to two small proteins called cellular RA-binding protein (CRABP) I and II, but until recently, this was thought not to play a major role in the transcriptional activity of RA. Most people assumed that the function of the binding proteins was to keep RA, which is a lipophilic compound, in solution.

Noa Noy and her team at Cornell University (http://www.cornell.edu) were intrigued by the fact that the cell should use two proteins to perform this simple task. They therefore wanted to see what specific functions these binding proteins might have. In 1999, they reported that CRABPII, but not CRABPI, actually enhances the ability of RAR to upregulate its target genes [1], and earlier this year, they showed how this was achieved. Their studies revealed that the cytosolic CRABPII protein moves to the nucleus once bound to RA. There, it interacts with RAR, and this interaction augments the transcriptional activity of RAR (Fig. 1) [2].

'These results are undoubtedly exciting,' says Lucia Altucci of the Second University of Naples (http://www.unina2.it). 'The observation that CRABP-II enhances the transcriptional activity of RARs by directly 'channeling' the ligand to the receptor introduces a novel concept into the present schemes of ligand action.'

Implications for treatment

Noy and colleagues then began to wonder whether the ability of CRABPII to enhance the transcriptional activity of RA will also result in increased therapeutic activity. They tested this hypothesis by

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