Alzheimer's and the immune system

Alzheimer's disease is one of the most feared—and most prevalent—afflictions of the elderly, affecting as many as half of the population over 85 years old. Much of the fear of this disease stems from its bleak prognosis and inadequate treatment, both symptoms of our cursory understanding of the disease. Now, a new study on a mouse model of Alzheimer's sheds light on the progression of this haunting affliction that may help arrest its development.

In the study, led by Andrew Luster at Harvard Medical School (Boston, MA), researchers crossed two kinds of transgenic mice. The first type of mouse, an established murine model of Alzheimer's disease, expresses human amyloid precursor protein (APP), which is transformed in the brain into β-amyloid, deposits of which are the hallmark of Alzheimer's. The second type of mouse is deficient in CCR2 ($CCR2^{-/-}$), a receptor involved in chemotaxis that is expressed by microglia and monocytes, two kinds of immune cells that can be found in the brain.

Luster and his team crossbred these two types of mice, producing offspring that express human APP but lack CCR2 (APP-$CCR2^{-/-}$). They found that these mice accumulated significantly more β-amyloid in their brains and had starkly higher mortality as compared to mice expressing human APP alone (*Nat. Med.*, April). Moreover, the study also showed that the APP-$CCR2^{-/-}$ mice had 80% fewer microglia and monocytes in their brains, suggesting that the increased accumulation of β-amyloid—and resulting mortality—is related to the absence of these immune cells.

Presumably, the missing CCR2 is responsible for directing the microglia and monocytes to migrate from the blood and other areas to sites of β-amyloid deposits in the brain. This conclusion squares with another finding that CCL2, the main chemoattractive ligand for CCR2, is increased in humans with Alzheimer's disease. But even if this hypothesis is correct, much still remains unsolved. For instance, if microglia and monocytes are indeed involved in clearing β-amyloid deposits from the brain, is malfunctioning CCR2, at least in part, responsible for Alzheimer's? Or, can clinical intervention aid monocytes and microglia to reverse (or at least slow down) the memory loss and other symptoms associated with Alzheimer's? Hopefully, continued investigation of CCR2 will yield life-altering answers to these and other questions about this vexing disease.

Owen Young

PROTECTING THE TRACT

The emergence in recent years of antibiotic-resistant bacterial strains has made the treatment of many types of infection more difficult. As a result, researchers are striving to develop more innovative ways to treat what have been routine maladies. A new study of the infection route of uropathogenic *Escherichia coli* (UPEC), the bacterium most commonly responsible for urinary tract infections (UTIs), does just that by building on a more detailed understanding of bladder physiology.

There are nearly one hundred million UTIs in the world every year, the vast majority of which are caused by UPEC. Perhaps even more troubling, one in four women who are treated for UTIs with antibiotics have a recurrent infection within six months. This result, coupled with the increasing impotence of many antibiotics, is an uncomfortable prospect for many patients and doctors.

Brian L. Bishop of Duke University Medical Center (Durham, NC) decided to investigate the underlying mechanism of UPEC invasion of the bladder. UPEC invasion is contingent on the bacteria attaching themselves to plaques of proteins in the bladder epithelium called uroplakins. These plaques form initially as discoidal vesicles inside the bladder cells that later embed in the cells' apical surface by exocytosis. Prior work by other researchers on the protozoan *Trypanosoma cruzi* has demonstrated that infection with this parasite is often mediated by secretory lysosomes, membrane-bound cellular compartments similar to the discoidal vesicles of the bladder cells. Bishop and his colleagues reasoned that UPEC invasion and recurrence might be aided by a similar mechanism.

To test this theory, Bishop looked at mice that had been infected with UPEC and found that the bacteria colocalized with molecular markers for the discoidal vesicles (*Nat. Med.*, April). Essentially, their findings revealed that the bacteria enter the bladder cells by invading membrane invaginations produced as the discoidal vesicles fuse with the apical membrane to form the plaques. The bacteria themselves end up shielded within discoidal vesicles inside the bladder cells.

Based on their findings, the researchers proposed a potential UTI treatment: taking advantage of the fact that exocytosis of the vesicles can be induced by an increase in the cellular concentration of cyclic adenosine monophosphate (cAMP), Bishop and his coworkers treated UPEC-infected mice with forskolin, a molecule long recognized to increase cAMP concentrations. This treatment successfully eliminated the mouse UTIs. Forskolin is already used to help treat asthma, glaucoma, and other diseases; researchers hope that forskolin treatment of UTIs will augment antibiotic treatment in humans as well.

Owen Young