Reports on Scientific Meeting

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Learning from lesions: leprosy as a model for immune responses in skin

Speaker: Dr. R. L. Modlin

Leprosy, as an ancient disease, has brought along pain and suffering to human. Yet in the recent years, the disease offers many clues about the immune responses in skin. Dr. Robert L. Modlin during his presentation in the Marion B. Sulzberger Memorial Award Lectureship, shared what researchers have learned about this immune response.

As the chief of dermatology at the University of California in Los Angeles, Dr. Modlin said, "leprosy provides an extraordinary clinical model for studying endoregulation in skin. That's because the disease is not a single clinical entity but presents as a spectrum of clinical manifestations that correlate with the level of the immune response against the pathogen mycobacterium leprae."

Leprosy can present as either tuberculoid or lepromatous form. Tuberculoid leprosy manifests itself with fewer skin lesions in infected patients. The lepromatous form results in multiple skin lesions and an enormous number of intracellular leprae bacillae, and the immune system is ineffective in controlling the infection. Cell mediated immunity is strong in tuberculoid patients, but such T-cell responses are impaired in lepromatous patients.

Dr. Modlin further distinguished the differences between the adaptive immune response and the innate immune systems. The adaptive immune response involves the selection and expansion of immune cells that are specific to a particular pathogen. These include the development of memory, through the involvement of developing T-cell and their active role in host defense. On the other hand, the innate immune system contains those immune defense mechanisms that pre-exist in all individuals. The innate system can act within minutes of infection through macrophage and natural killer cell responses and target nonspecifically to all invading pathogens.

In tuberculoid lesions, CD4+, TH1 cells, CD8+ cytotoxic T-cell, dendritic cells and macrophages are the key cells in the lesions that control infection. Interleukin (IL) 12 and the Toll-like receptors are the key molecules for the innate system. The mycobacterial lipoproteins are potent stimulators of IL-12 production by human macrophages, and that induction is mediated through Toll-like receptors on the macrophages. Toll-like receptor enhances the transcription of nitric oxide synthase and the production of nitric oxide which is a

powerful antimicrobial agent. In the adaptive system, interferon gamma, CD1 and granulysin are the key molecules. "The result of these cells and these molecules is cell mediated immunity controlling infection," Dr. Modlin noted.

Different immune responses are seen in lepromatous lesions. In lepromatous lesions, the key cells are the CD8+, TH2 cells and monocytes. The key molecule for the innate systems are IL-10, and for the adaptive system, IL-4. The results of this pattern of cells and molecules appear to be the development of a specific tolerance for mycobacterium leprae.

As a result of identifying the key patho-immunological mechanisms involved in tuberculoid and lepromatous lesions, new clues in developing potential therapies are at the doorsteps. "These cells and molecules provide targets for intervention, and it should be possible to use this information for new treatments for leprosy and other skin diseases" Dr. Modlin said.

According to Dr. Modlin, there is another compelling reason to study leprosy, in addition to gaining insight about immune response in skin. The disease affects about one million people worldwide, making it a health and economic burden on developing countries. The incidence of leprosy has in fact increased in the past 17 years from 550,000 new leprosy patients in 1995 to 760,695 new patients in 2000. Dr. Modlin commented that the increase in new leprosy patients indicated that multi-drug therapy had had minimal impact on the number of new patients, and the leprae bacterium had also become resistant to some antibiotic therapies. "This underscores the need for new vaccine development, which can ultimately occur through identification of the protective immune response and understanding the mechanisms of tolerance", said Dr. Modlin.

Learning Points:

As a result of identifying the key cells and molecules involved in the pathogenetic mechanisms in tuberculoid and lepromatous leprosy, new interventional strategy and vaccine development targeting these cells and molecules will provide the breakthrough in the management of this ancient disease.

Symposium on psoriasis and update of therapies

Speakers: Drs. J. P. Callen, C. A. Elmets, S. R. Feldman, A. B. Gottlieb, H. Honigsmann, A. B. Kimball, G. G Krueger, M. Lebwohl and A. J. Theos

Patients with psoriasis have been asking for new treatments and therapies for years. In recent years, new biologic agents have been developed for the treatment of psoriasis that have the potential to improve the quality of life of the seven million psoriatic patients in USA, and benefit even more patients in the world.

Information about the science behind the new biologic therapies and how they are revolutionizing the treatment of psoriasis is discussed in the symposium. Studies show that psoriasis originates in the immune system and therefore many current treatments target that system. What is unique about biologic treatments is that they pinpoint certain immune responses that are involved in psoriasis, not the entire immune system, thereby creating fewer side effects for the patients and less damage to the immune system as a whole, as compared with the current conventional therapy.

Research has shown that the activation of T-cell is the key in triggering the development of psoriasis. Once activated, these cells release cytokines, which lead to rapid turnover and accelerated

proliferation of keratinocytes and setting off other reaction that leads to psoriatic lesions forming on the skin. Various biologic therapies attempt to block this initial T-cell activation.

A variety of biologics, each with long and difficult generic names, have been developed. The nomenclature of these new biologics seems confusing, but Dr. Callen explained the rule very clearly. A drug that ends with "ximab" (e.g. infliximab) means that it is a chimeric monoclonal antibody. One like efalizumab that ends with "zumab" is humanized monoclonal antibody. An "umab" drug like adalimumab is a human monoclonal antibody. And finally, a drug ending in "cept" such as etanercept is a receptor-antibody fusion protein.

Alefacept is the first biologic to be approved by the Food and Drug Administration (FDA) for the treatment of adult psoriasis with moderate to severe disease who are candidates for systemic therapy or phototherapy. It is an immuno-suppressive dimeric fusion protein that consists of the extracellular CD2- binding portion of the human leukocyte function antigen-3 (LFA-3) linked to the Fc portion of human IgG1. This biologic works by destroying activated T-cells especially memory T-cells, which are involved in the pathogenesis of psoriasis, thereby stopping the early cycle of psoriasis. It has negligible effects on naive T-cells, natural killer cells, and B-lymphocytes. In a recent study by Vaishnaw et al, patients received a 12-week course of alefacept. This drug is given intravenously (7.5 mg IV) or through intramuscular (15 mg IM) injection every week. After 12-weeks, more than 30 percent of patients had a very significant improvement in their psoriasis with a reduction on the Psoriasis Activity and Severity Index (PASI) of greater than 75 percent. Even more patients improved when PASI reduction of greater than 50 percent were considered. In addition, the level of improvement continued long after the course of treatment was finished. In fact, improvement after a course of alefacept has been shown to last for an average of eight months or longer, depending on the length of treatment. Lymphopenia, increased risk of infection and possibly malignancies such as basal or squamous cell carcinoma have been reported. Among 1357 patients who received alefacept in one study, 25 patients were diagnosed with 35 treatment-related malignancies. The majority of them were basal (n=6) or squamous cell carcinoma (n=17) of the skin. Three cases of lymphoma were observed, one being non-Hodgkin's and two Hodgkin's lymphoma.

Etanercept is the second biologic that is FDA-approved for the treatment of psoriatic arthritis and is currently in phase III trials for the treatment of cutaneous psoriasis. It is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75kd tumour necrosis factor (TNF) receptor linked to the Fc portion of human IgG1. Etanercept blocks TNF, hence prevents the initiation of the kerationocyte excessive proliferation. In preliminary studies in patients with extensive psoriasis, twice weekly subcutaneous injections (25 mg SC) with etanercept resulted in more than half of the patients having a reduction on their PASI of up to 75 percent. More than 70 percent of patients experienced a reduction on the PASI of up to 50 percent. Etanercept has a relatively slow onset of action, with significant improvement being seen in about three months.

Furthermore, efalizumab and infliximab are two other biologics that are currently in phase III testing with the FDA and both have been shown to improve psoriasis dramatically.

Efalizumab is a humanised monoclonal IgG1 antibody to CD11a, the alpha chain of leukocytes function associated antigen-1(LFA-1). It interferes with the migration of T-cell to the skin and their activation in tissue and hence provides potential benefit for patients with psoriasis. It has an advantage of relatively rapid onset of therapeutic effect. It is given by subcutaneous injection (2 mg/kg) once a week. Gottlieb et al, in an open-label study demonstrated significant improvement of

PASI in patients receiving up to 60 weeks of continuous efalizumab treatment. There were no significant side effects except non-specific headache, common cold, chills, fever and nausea.

As TNF-alpha is regarded as a key factor in pathophysiology of psoriasis, infliximab, which is another anti-TNF-alpha monoclonal antibody, also blocks TNF and halts the psoriatic proliferation of keratinocytes. The drug can be given intravenously (3-7.8 mg/kg) in office setting over a course of several weeks intermittently to control severe disease. A small-scale open-label preliminary study by Vath et al showed significant improvement in psoriatic disease in all six patients. It appeared to have a more rapid response time of about 10 weeks. Two patients experienced mild adverse reactions including rash and reactivation of Epstein-Barr virus. Further investigation into the role in infliximab in the treatment of psoriasis is warranted.

Dr. Krueger commented that these biologics might become the treatment of choice, especially for those patients who are not controlled by the current therapies or the latter have caused unacceptable side effects. One important consideration for these biologics is the expensive cost. "The costs of these treatments may be prohibitive for some patients, since it is very expensive to bring these therapies to market," said Dr. Krueger, "but these treatment are a positive step forward in treating this skin disease because they maintain long-term remission while improving the patient's quality of life".

Learning points:

What is unique about the new biologic treatments for psoriasis is that they pinpoint certain immune responses that are involved in the disease, not the entire immune system, thereby creating fewer side effects for the patients and less damage to the immune system as a whole. Alefacept, etanercept, efalizumab, infliximab are four of the emerging promising biologic treatments for psoriasis.