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Highlights From the Latest in Diabetes Research

IL-7Rα Blockade: A New Therapy for Type 1 Diabetes?

Type 1 diabetes (T1D) is a complex disease whose pathogenesis involves islet-specific autoreactive T cells that destroy insulin producing β-cells in the pancreas. Autoreactive T cells are usually under tight regulation, and exactly how these cells overcome the inhibition that leads to disease is not well understood. Recent studies have focused on the actions of interleukin (IL)-7, a crucial cytokine for T-cell homeostasis that may also have a role in reversing suppressor functions in T cells, thus promoting T1D. Recently, two laboratories examined IL-7's actions through the IL-7 receptor-α (IL-7Rα) in T1D using IL-7Rα antibodies in NOD mice. Both groups demonstrated prevention and reversal of T1D in NOD mice by IL-7Rα blockade. IL-7Rα blockade upregulated expression of the negative regulator programmed death 1 (PD-1) on the cell surface of $CD4^+$ and $CD8^+$ T effector and memory cells in the pancreas. PD-1 and its ligand PD-1L are tightly correlated with maintaining tolerance of effector T cells in inflamed tissues and protecting against autoimmune diabetes. Previous studies have correlated loss of PD-1 in knockout NOD mice with increases in IFN-γ production and progression to diabetes. Both groups demonstrated that even with blockade of the IL-7Rα, use of an anti–PD-1 antibody led to diabetic relapse, providing evidence for a role of PD-1 in the therapeutic effects of IL-7Rα blockade.

Further studies in NOD mice from the Lee laboratory demonstrated that IL-7 increased T-cell development with a concomitant decrease in PD-1 expression, whereas the anti–IL-7Rα antibody resulted in less proliferative effector T cells and increased PD-1 expression. The investigators propose that the therapeutic activity of the IL-7Rα antibody results from a reduction in IFN-γ^+ effector T cells and upregulation of PD-1. They suggest further work is needed to uncover the molecular mechanism of PD-1 upregulation and reduction of effector T-cell proliferation after IL-7Rα blockade. Similarly, Penaranda et al. demonstrated that memory and effector T-cell survival is not compromised by the IL-7Rα blockade; rather the lack of IL-7 action leads to diabetogenic T-cell tolerance, underscoring the therapeutic efficacy of the IL-7Rα antibody. Absence of IL-7 action causes upregulation of PD-1, whose induction in infiltrating pathogenic T cells could prevent further islet cell loss. The investigators suggest that effector and memory T cells are a likely mechanism for autoimmunity once T1D has begun. Since effector and memory T cells are more difficult to control, there is a need for alternative therapeutic approaches. IL-7 signaling is a promising target because these T cells depend to a large extent on IL-7 for activation. Studies from these two laboratories have provided a previously unidentified link among IL-7, PD-1, and autoimmunity, as well as evidence for a novel therapeutic strategy for T1D. — *Eileen Resnick, PhD*

- Lee et al. Anti–IL-7 receptor-α reverses established type 1 diabetes in nonobese diabetic mice by modulating effector T-cell function. Proc Natl Acad Sci U S A 2012;109:12674–12679
- Penaranda et al. IL-7 receptor blockade reverses autoimmune diabetes by promoting inhibition of effector/memory T cells. Proc Natl Acad Sci U S A 2012;109:12668–12673

As Little as 20 Minutes of School-Based Aerobic Exercise Yields Compelling Results in Overweight and Obese Children

National data are clear about trends in childhood obesity in the U.S.: the percentage of obese children aged 6–11 years increased from 7% in 1980 to nearly 20% in 2008. Among obese adolescents aged 12–19 years, the prevalence increased from 5% to 18% during the same period. The Diabetes Prevention Program, as well as similar studies in children, indicates that lifestyle modification can reduce the metabolic risk associated with obesity, thereby reducing the risk of diabetes. Despite widespread agreement on the benefits of exercise in children, there are no available data on exercise dose that can be used to formulate public health recommendations for risk modification in overweight and obese children. A new study by Davis et al. addressed this basic question by randomizing 222 overweight or obese sedentary children to one of three conditions: high-dose aerobic training (40 min per day/5 days per week), low-dose aerobic training (20 min per day/5 days per week), or a control group of children who engaged in usual physical activity. Six cohorts of approximately 30–40 children were studied over a period of 4 years. The intervention was offered after school, and each cohort of participants was followed for approximately 13 weeks during the course of one semester. At the end of follow-up and relative to the control group, insulin resistance, body fat, and visceral fat were more favorable in both the high- and low-intensity exercise groups. No significant differences in these measures were observed between the high- and low-intensity groups, and no interactions were observed according to key factors such as sex, race, and family history of diabetes. Several features of this study are noteworthy: it achieved a 94% adherence rate, the intervention did not involve dietary restrictions, the follow-up period that yielded these results was relatively short, the impact of the intervention was the same for

boys and girls and black and white children, and the intervention was conducted in a school-based setting. Although this was an efficacy study, the study's characteristics relate favorably to the potential of an intervention of this type to be developed into an effectiveness study to determine whether this compelling proof of concept can be successfully implemented in practice. Given that only 20 min per day during a school day would be required to generate these results, the study by Davis et al. represents a meaningful step forward toward identifying the characteristics of feasible school-based exercise recommendations aimed at directly addressing the metabolic consequences of the obesity epidemic in children. — *Helaine E. Resnick, PhD, MPH*

■ Davis et al. Exercise dose and diabetes risk in overweight and obese children: a randomized controlled trial. JAMA 2012;308:1103–1112

An Integrated Encyclopedia of DNA Elements in the Human Genome

Although it has been over 10 years since the completion and release of the full human DNA sequence by the Human Genome Project, the functions of nearly all of the 3 billion base pairs of sequence have remained much of a mystery. The summer of 2012 marked the first major milestone in efforts to understand the meaning of the genomic DNA sequence with the release of major findings from the Encyclopedia of DNA Elements (ENCODE) project. Numerous ENCODE investigators, representing many different research centers, have systematically mapped functional elements across the entire genome, including transcribed regions, transcription factor binding sites, and regions affected by the structure and modification of chromatin. Among the many illuminating results of this astonishing feat was the announcement that over 80% of the genome has now been assigned biochemical functions, thus dispelling the notion that much of the intergenic portion of the genome is "junk" or "filler." ENCODE thus provides the first close-up look at the complexities of gene regulation. This new research has extensive implications for research on diabetes and other complex diseases. ENCODE will provide the basic tools to understand the molecular mechanisms of these conditions, thereby facilitating our understanding of how thousands of disease-associated SNPs affect gene function and ultimately disease risk. In turn, this knowledge can be used to design better therapies and to personalize treatments. The ENCODE project is an exceptionally valuable scientific resource whose potential for influencing the course of human disease will be played out for years to come. — *Braxton D. Mitchell, PhD, MPH*

■ The ENCODE Project Consortium. An integrated encyclopedia of DNA elements in the human genome. Nature 2012;489:57–74

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