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nucleotide polymorphisms available for high throughput genotyping will improve, and detailed analysis of the role of copy number variants in these diseases will shed new light on the pathogenesis of these common endocrinopathies.

Advances in Type 1 Diabetes Therapeutics: Immunomodulation and β -Cell Salvage 303

Frank Waldron-Lynch and Kevan C. Herold

Refinements in our understanding of the pathogenic mechanisms of Type 1 diabetes from studies of animal models and clinical observation have led to new clinical trials to prevent disease progression and restore the loss of β -cells that defines the disease. Antigen-specific agents have shown initial promise and non-antigen-specific agents now have improved safety compared with older agents. In addition, preclinical studies with other agents have shown efficacy. Ultimately, a combination of immunologic and cellular therapies may be needed to restore metabolic control. Agents that augment recovery of dysfunctional β -cells, and other compounds that may be able to induce β -cell replication, are logical additions once immune tolerance is achieved.

The Thyroid-Stimulating Hormone Receptor: Impact of Thyroid-Stimulating Hormone and Thyroid-Stimulating Hormone Receptor Antibodies on Multimerization, Cleavage, and Signaling 319

Rauf Latif, Syed A. Morshed, Mone Zaidi, and Terry F. Davies

The thyroid-stimulating hormone receptor (TSHR) has a central role in thyrocyte function and is also one of the major autoantigens for the autoimmune thyroid diseases. We review the post-translational processing, multimerization, and intramolecular cleavage of TSHR, all of which may modulate its signal transduction. The recent characterization of monoclonal antibodies to the TSHR, including stimulating, blocking, and neutral antibodies, have also revealed unique biologic insights into receptor activation and the variety of these TSHR antibodies may help explain the multiple clinical phenotypes seen in autoimmune thyroid diseases. Knowledge of the structure/function relationship of the TSHR is beginning to provide a greater understanding of thyroid physiology and thyroid autoimmunity.

Toward Better Models of Hyperthyroid Graves' Disease 343

Selçuk Dağdelen, Yi-chi M. Kong, and J. Paul Banga

Graves' disease affects only humans. Although it is a treatable illness, medical therapy with antithyroid drugs is imperfect, showing high rates of recurrence. Furthermore, the etiology and treatment of the associated ophthalmopathy still represent problematic issues. Animal models could contribute to the solution of such problems by providing a better understanding of the underlying pathogenesis and could be used for evaluating novel therapeutic strategies. This article discusses the pursuit of a better experimental model for hyperthyroid Graves' disease and outlines how this research has clarified the immunology of the disease.

Treatment of Graves' Hyperthyroidism: Evidence-Based and Emerging Modalities 355

Laszlo Hegedüs

Currently there are three well-established treatment options for hyperthyroid Graves' disease (GD): antithyroid drug therapy with thionamides (ATD), radioactive iodine treatment with ^{131}I , and thyroid surgery. This article reviews the current evidence so the reader can evaluate advantages and disadvantages of these treatment modalities. Surgery is rarely used, except for patients who have a large goiter or ophthalmopathy. Fewer than 50% of patients treated with ATD remain in long-term remission. Therefore, radioactive iodine is used increasingly. No data as yet support the routine use of biologic therapies (eg, rituximab). Prospective, randomized studies comparing available and any novel therapeutic options for GD are needed. The focus of these studies should include, but not be limited to, cost and quality of life.

Thyroid-Associated Orbitopathy: Who and How to Treat 373

Jane Dickinson and Petros Perros

Thyroid-associated orbitopathy is the most frequent and troublesome nonthyroidal complication of Graves' disease. It is mandatory to determine whether sight-threatening orbitopathy is present, as this requires prompt and aggressive treatment. Therapies for non-sight-threatening disease range from supportive measures only to medical therapies for active eye disease and surgical rehabilitation for burnt-out disease. Intravenous steroids and orbital radiotherapy are the mainstays of medical therapy. Rehabilitative surgery is frequently a staged process that may involve sequentially: orbital decompression, strabismus surgery, and eyelid procedures. Smoking cessation is recommended at all disease stages. Treatment within a multidisciplinary team consisting of both endocrinologists and ophthalmologists may lead to optimal patient outcomes.

Immunology of Addison's Disease and Premature Ovarian Failure 389

Eystein S. Husebye and Kristian Løvås

Autoimmune Addison's disease and autoimmune ovarian insufficiency are caused by selective targeting by T and B lymphocytes to the steroidogenic apparatus in these organs. Autoantibodies toward 21-hydroxylase are a clinically useful marker for autoimmune Addison's disease. Autoantibodies to 21-hydroxylase are found in premature ovarian insufficiency, but others also can be present, notably antibodies against side-chain cleavage enzyme. The autoimmune response primarily targets the theca cells, yielding elevated concentrations of inhibin, which is emerging as a useful diagnostic marker for autoimmune etiology of ovarian insufficiency. Little is known about its immunogenetics, but in contrast to Addison's disease, several experimental models of autoimmune premature ovarian insufficiency are available for study.

Fine Tuning for Quality of Life: 21st Century Approach to Treatment of Addison's Disease 407

Nicole Reisch and Wiebke Arlt

Despite treatment with glucocorticoids and mineralocorticoids, the ability to work and quality of life of patients who have adrenal insufficiency

remains low. There are no helpful objective measures of optimal glucocorticoid replacement, so this is best achieved by careful clinical assessment. Adequacy of mineralocorticoid replacement may be judged by assessing postural change in blood pressure, serum electrolytes, and plasma renin activity. Novel delayed-release and sustained-release formulations of hydrocortisone seem to more closely mimic diurnal serum cortisol rhythms than conventional hydrocortisone tablets. Such preparations are currently being evaluated and may play a role in management of patients who have adrenal insufficiency.

Diagnosis and Management of Polyendocrinopathy Syndromes

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Catherine J. Owen and Tim D. Cheetham

The autoimmune polyendocrinopathy syndromes are variable in presentation and can be challenging to diagnose and manage. Diagnosis of the type 1 autoimmune polyendocrinopathy syndrome can be difficult at an early age when often only one manifestation is present, and it may take years for others to appear. Increased awareness of polyendocrinopathy syndromes, combined with analysis of specific autoantibodies and molecular genetics, should help earlier diagnosis of these conditions and prevent serious complications. Further definition of susceptibility genes and autoantigens, as well as a better understanding of the pathogenesis, is required to improve the diagnosis and management of these patients.

Anti-Parathyroid and Anti-Calcium Sensing Receptor Antibodies in Autoimmune Hypoparathyroidism

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Edward M. Brown

The parathyroid glands are an infrequent target for autoimmunity, the exception being autoimmune polyglandular syndrome type 1, in which autoimmune hypoparathyroidism is the rule. Antibodies that are directed against the parathyroid cell surface calcium-sensing receptor (CaSR) have recently been recognized to be present in the serum of patients with autoimmune hypoparathyroidism. In some individuals, these anti-CaSR antibodies have also been shown to produce functional activation of the receptor, suggesting a direct pathogenic role in hypocalcemia. Additionally, a few hypercalcemic patients with autoimmune hypocalciuric hypercalcemia owing to anti-CaSR antibodies that inhibit receptor activation have now been identified. Other novel parathyroid autoantigens are starting to be elucidated, suggesting that new approaches to treatment, such as CaSR antagonists or agonists (calcilytics/calcimimetics), may be worthwhile.

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