Molecular Gastrointestinal Scintigraphy

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24.1 Introduction

Over the past 30 years, the description of the scintigraphic procedures to perform gastrointestinal imaging studies and their findings in multiple diseases have been described in journal articles and textbook chapters (Urbain et al. 2000, 2002). The aim of this contribution is to provide the nuclear medicine scientist with the basic genetic knowledge of various diseases as it relates to the gastrointestinal tract and may affect the result of gastrointestinal scintigraphic studies. First, the basic, molecular and genetic abnormalities of diseases affecting the motility of the gastrointestinal tract are explained. The molecular onco-genesis of gastrointestinal tumors is then described and illustrated with positron emission tomography (PET) examples. The neuroendocrine system of the gastrointestinal tract is then reviewed with a “molecular scope”. Finally, the most promising avenue in molecular gastrointestinal scintigraphy is evoked.

24.2 Genetic Diseases and GI Transit Abnormality

24.2.1 Salivary Glands

The diagnosis of Sjögren syndrome requires the documentation of decreased lacrimal function, dryness in the mouth and evidence of autoimmunity dysfunction. It is the second most frequent autoimmune disorder after rheumatoid arthritis. The scintigraphic salivary gland challenge test with pertechnetate has proven to be very useful as part of the diagnostic workup for this syndrome.

Autoimmune disorders are typically classified in two groups: the organ-specific diseases and the systemic diseases. In organ-specific autoimmunity (e.g. Hashimoto’s thyroiditis, Grave’s disease, multiple sclerosis, etc.), antigens peculiar to a cell type are the target of an aggressive immune response. The non-organ-specific disorders include diseases such as systemic sclerosis, rheumatoid arthritis and Sjögren syndrome.

These diseases of systemic autoimmunity occur in individuals genetically predisposed. In these individuals, one or multiple environmental influences trigger T-cell dysregulations and the pathogenic production of autoantibodies reacting to self antigens. The genes that regulate normal immune function and play a key role in autoimmunity encode the major histocompatibility complex (MHC) or human lym-
phocyte antigen (HLA) on chromosome 6, the T-cell receptors (TCR), immunoglobulins, the complement and the antigen processing and presentation molecules. Since women are affected twice as often as men, the sex-related genes are also involved.

The MHC gene products are grouped in two categories. The class I molecules are present on the surface of most nucleated cells. They bind short peptides arising from the cytoplasm of the cell and present them to cytotoxic T cells. MHC class II molecules, also designated DR and DQ, are present on monocytes, B cells and other antigen-presenting cells. They bind larger peptides derived from extracellular proteins and interact with T-cell receptors on CD4+ lymphocytes that regulate the immunoglobulin production.

The HLA DR3 antigen has been associated with Sjögren syndrome. Antinuclear antibodies are present in approximately 90% of patients with SS. Antibodies to SS-A (anti-Ro) and to SS-B (anti-La) are also found in patients with SS.

24.2.2 Esophagus

The esophagus is a long muscular tube which extends from the cricoid cartilage to the stomach. The proximal third of the esophagus consists of striated muscle, the distal third is composed of smooth muscle, and the middle portion is a transitional mixture of the two. The upper esophageal sphincter, the body, and the lower esophageal sphincter are the distinguishable anatomic structure. The coordinated function of these structures conveys swallowed liquid and food from the mouth to the stomach and clears residual substances. Esophageal motility follows a precisely coordinated pattern characterized by primary, secondary and tertiary contractions.

Esophageal motility disturbances are classically categorized into primary or secondary disorders depending on the pathophysiologic mechanisms. Achalasia, diffuse esophageal spasm, nutcracker esophagus and non-specific motor disorders account for the so-called primary esophageal motility disorders. Neuromuscular and connective tissue disorders encompass diseases such as scleroderma, systemic lupus erythematosus, Raynaud's disease and dermatopolymyositis. Vertebral cervicopathy and diabetes also may exhibit esophageal transit abnormality. Anatomic alterations due to tumor, diverticula, surgery, trauma, infection may also lead to secondary motor disorders of the esophagus.

Systemic sclerosis (SS) is a generalized vascular and fibrotic autoimmune disease that affects multiple organs including the gastrointestinal tract. Diminished smooth muscle motor activity of the distal two-thirds of the esophagus is the most frequent finding and results in dysphagia and esophageal reflux. Gastric emptying might be delayed; small bowel involvement results in malabsorption and bacterial overgrowth. Colonic involvement results in stasis, constipation and diverticula. As for all autoimmune diseases, the pathogenesis is felt to involve interacting genetic and environmental factors. The molecular pathophysiology of systemic sclerosis is incompletely understood and the primary etiologies remain a mystery. Hypotheses include: an altered ability of T lymphocytes to distinguish between self and non-self antigens, the clonal expansion of self-reactive T cells involving the major histocompatibility complex (MHC) or the heteromultimeric T-cell receptor (TCR). Immunologic features of SS include the presence of specific autoantibodies against centromeres, topoisomerase I, RNA polymerase I, II, III, fibrillarin, a ribonucleoprotein (U3RNP), U1RNP. Cytokines such as interleukins IL-1, IL-6, IL-8, TGF-β, PDGF, fibronectin, endothelin and VEGF have also been implicated in the pathogenesis of the disease. The antitopoisomerase I autoantibody is associated with DR5.

Polymyositis (PM) and dermatomyositis (DM) are autoimmune inflammatory diseases of the striated muscles that may present distinctively or with other autoimmune disorders such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) or systemic sclerosis. The peak onset of this disease is in the fifth decade. Most autoimmune diseases have been associated with genes in the class II of the MHC. PM and DM have been associated with the DR3 antigen of the MHC.

24.2.3 Stomach

The human stomach consists of two functionally integrated, but electro-mechanically distinct, portions. The proximal stomach, which encompasses the fundus and the proximal corpus, functions as a reservoir for solid and liquid food and controls the emptying of liquids. The distal stomach, which includes the mid and distal corpus and the antrum, is characterized by peristaltic contractions that break down solid food into small particles and mix them with gastric