MONOCLONAL ANTIBODIES TO PANCREATIC LANGERHANS ISLETS: IMMUNOCHEMISTRY AND APPLICATIONS

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ABSTRACT

Monoclonal islet cell antibodies have begun to facilitate the identification and biochemical characterization of cellular differentiation molecules. We have developed a series of murine monoclonal antibody probes directed towards islet endocrine cells. Utilizing these antibodies we identified and biochemically characterized several islet cell antigens. Many islet cell antibodies appear to react with unique carbohydrate residues on their antigen molecules. As demonstrated by immunocytochemistry, islet cells share several monoclonal antibody-defined antigens and antigenic determinants with other neuroendocrine cell types indicating common modes of functional differentiation and specialization.

Some applications of the monoclonal islet cell antibodies in diagnostic pathology as markers for neuroendocrine tumors as well as for the analysis of the specific biologic function of monoclonal antibody-defined antigens illustrate the usefulness of monoclonal antibodies as probes to elucidate complex molecular mechanisms involved in normal and pathological endocrine cell function.

INTRODUCTION

Over the last decade it has become increasingly clear that Type I diabetes mellitus (DM) results from a slowly progressive, immunologically mediated, islet beta cell destruction, initiated in genetically predisposed individuals by as yet undefined (environmental or non-genetic) factors (1-8).
A prolonged asymptomatic preclinical stage of progressive beta cell destruction associated with specific immunological abnormalities (islet cell antibodies, activated T cells) precedes the onset of overt Type I DM by several years (2-5). Autoimmune mechanisms being involved in the beta cell destructive process in Type I DM are indicated by several lines of evidence: 1) the demonstration of lymphocytic infiltration of the islets ("insulitis") early in the course of the disease, 2) clinical association of Type I DM with other established or putative autoimmune diseases (both endocrine and non-endocrine), 3) the increased prevalence of organ-specific autoantibodies (thyroid, gastric parietal cells, adrenal gland), 4) the detection of a family of islet-cell antibodies (islet cell cytoplasmic antibody - ICA, islet cell cytoplasmic complement fixing antibody - CF-ICA, islet cell surface antibody - ICSA, and islet cell cytotoxic antibody), 5) demonstration of abnormalities of cell-mediated immune function, 6) association with certain antigens of the major histocompatibility locus, and 7) studies in animal models of Type I DM (for review see 9 and 10; 11-15).

Despite these recent advances in our knowledge, the basic mechanism of the autoimmune beta cell destruction remains poorly understood. The selectivity of the immune response which leads to the beta cell destruction in Type I DM appears to be conferred by unique differentiation antigens ("target" autoantigens) expressed by the pancreatic islet beta cells. The autoantibody detected by indirect immunofluorescence staining of a normal human pancreatic frozen section by sera of patients with newly diagnosed Type I DM has been conventionally referred to as the cytoplasmic islet cell antibody (ICA), based on its presumptive binding to antigens located within the cytoplasm of the islet cells (14). These autoantibodies selectively bind to all the endocrine pancreatic cells, but not to the exocrine acinar pancreatic cells, ductular cells or the stromal connective tissue cells. Anti-islet autoantibodies have also been detected by the surface staining of viable human and rodent pancreatic islet cells, and these have