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Review

Primary biliary cirrhosis and the nuclear pore complex

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ABSTRACT

Experimental models of autoimmune diseases have led to the conclusion that an immune response to nuclear antigens is a sentinel marker for loss of tolerance and potential tissue damage. Various proteins are targets of antinuclear antibodies in a variety of autoimmune diseases, ranging from systemic rheumatologic disorders to diseases affecting specific organs such as the liver. Autoantibodies against specific nuclear constituents have also been used as probes to understand the structure and the function of the targeted components and their relevance to disease pathogenesis. Approximately a quarter of patients with primary biliary cirrhosis (PBC) have antibodies targeting proteins of the nuclear pore complex (NPC), a multi-protein structure that mediates molecular transport across the nuclear envelope. Autoantibodies against the integral membrane glycoprotein gp210 and nucleoporin p62 appear to be highly specific for PBC, an autoimmune disease characterized by progressive destruction of intrahepatic biliary epithelial cells. This review discusses the diagnostic and clinical relevance of anti-NPC antibodies in PBC and the possibility that this autoimmune response may arise as a result of molecular mimicry.

Contents

1. Introduction

Loss of immunological tolerance to the nucleus is among the best-studied topics in autoimmunity, largely due to the fact that antinuclear antibodies (ANA) are frequently present in a variety of autoimmune diseases [1–11]. However, the mechanisms responsible for the induction of immune responses against distinct nuclear antigens and their relevance to specific diseases remain elusive.

Abbreviations: AMA, antimitochondrial antibodies; ANA, antinuclear antibodies; IIF, indirect immunofluorescence microscopy; NE, nuclear envelope; NPC, nuclear pore complex; Nup, nucleoporin; PBC, primary biliary cirrhosis; PDC-E2, E2 subunit of mitochondrial pyruvate dehydrogenase complex; SLE, systemic lupus erythematosus.

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ANA can be predictive of the future development of autoimmune disease and present years or possibly even decades before the onset of clinically evident disease [9]. To complicate the matter, ANA can be found at relatively low titers in up to 5% of "healthy" individuals, with the prevalence increasing with age. In some cases, ANA may be irrelevant to pathogenesis, possibly conferring protection from development of disease [12–14].

ANA are generally detected in clinical laboratories by indirect immunofluorescence microscopy (IIF) using as a substrate HEp-2 cell, a human laryngeal carcinoma line. HEp-2 cells are usually selected because they have large nuclei and cells in the preparations can be present in various stages of mitosis, allowing for discrimination of distinct staining patterns [15–18]. Nuclear fluorescence indicates not only the presence of ANA but also the localization of reactive antigens within the nucleus, as characteristic staining patterns are frequently correlated with specific diseases [15,18,19].

ANA in serum samples from patients with PBC often produce a rim-like pattern when examined by IIF, suggesting that the targets of the autoantibodies are components of the nuclear envelope (NE) [20–24]. A smooth rim-like fluorescence pattern suggests antibody recognition of an antigen of the nuclear lamina or inner nuclear membrane whereas a punctate pattern suggests that the recognized antigen is a component of the nuclear pore complex (NPC) [15,19]. Autoantibodies specific for constituents of the NE antibodies have also been described in other autoimmune diseases sometimes associated with PBC, such as Sjögren's syndrome [25]. Additionally, such autoantibodies are occasionally present in systemic lupus erythematosus (SLE) and mixed connective tissue disorders [26,27]. These findings have prompted a series of investigations to define the autoantigens of the NE in PBC and to attempt to dissect their role in pathogenesis.

1.1. The NE

The NE is a highly organized membranous structure [28] divided into the nuclear membranes (outer, inner and pore domains), NPCs and the nuclear lamina. The outer nuclear membrane is directly continuous with the rough endoplasmic reticulum and the perinuclear space separates the inner from the outer membrane. The inner and pore membranes contain unique sets of intrinsic and extrinsic proteins [28,29]. The lamins, intermediate filament proteins that form the nuclear lamina, are extrinsic proteins of the inner nuclear membrane. Some transmembrane proteins freely diffuse between the inner, outer and pore membrane domains of the NE without concentrating in any of them. NPCs are located at sites where the inner and outer membranes fuse to form the pore membranes. Most of the protein building blocks of the NPC are called nucleoporins, some of which are transmembrane proteins of the pore membrane and most of which are non-membrane proteins of the complex.

1.2. The NPC

The number of NPCs varies among different cell types of different species. Among mammals, there are approximately 3000 to 5000 NPCs per nucleus. During interphase, the passage of molecules from and to the nucleus occurs strictly via the NPC. It is ~100–120 nm in diameter with a central transport channel measuring ~40 nm in diameter. The aqueous central transport channel allows for the exchange of macromolecules including RNA, proteins and ribonucleoproteins across the nuclear envelope, a process assisted by soluble transport receptors [29,30]. NPCs are also involved in chromatin organization, control of gene expression and replication-coupled DNA repair [29]. Electron microscopy and more recently X-ray crystallography have helped elucidate the structure and unique architecture of NPCs, in addition to providing insight as to how these macromolecular structures regulate the bidirectional exchange of macromolecules between the cytoplasm and nucleus [29,31]. NPCs have a central doughnut-shaped central core with an eightfold rotational symmetry associated with cytoplasmic filaments and a nuclear basket, each composed of complexes of various nucleoporins (Fig. 1) [29,31]. This distinctive architecture gives to NPC the flexibility required for the dynamic macromolecular translocation [31–33].

NPCs were first described sixty years ago with the advent of electron microscopy; however, mechanistic details regarding their functions have only recently been elucidated [34–37]. The nucleoporins comprise a family of at least 30 different evolutionary conserved proteins [29,32,33,38,39]. Each nucleoporin exists in multiple copies, and approximately 500–1000 protein molecules are present in the fully assembled NPC. A nucleoporin is generically denoted as Nup, followed by a number that refers to its molecular mass. However, a uniform nomenclature has not yet been agreed upon and the molecular masses of nucleoporins vary among species. Several authors have adopted a classification based on the approximate localization within the NPC. This classification has led to six categories including: (A) integral membrane proteins of the pore membrane domain of NE; (B) membrane-apposed coat nucleoporins; (C) adaptor nucleoporins; (D) channel nucleoporins; (E) nuclear basket nucleoporins; and, (F) cytoplasmic filament nucleoporins.

1.3. Antibodies against gp210 in PBC

In the late 1980s, Lozano et al. [23] and Lassoued et al. [21] demonstrated that serum samples from patients with PBC give a rim-like pattern when examined by IIF and that the antibodies recognized a NE protein with a molecular weight of approximately 200 kDa. A subsequent study by Courvalin et al. identified this protein as gp210 [40]. Nickowitz et al. [41] expressed a full-length recombinant gp210 and showed that all serum samples from patients with PBC reacting with the 200 kDa protein recognized the recombinant protein, thus confirming the identity of gp210 as the 200 kDa target in PBC.

Gp210 is a type I integral membrane protein that anchors NPCs to the pore membrane [42,43]. It has a cytoplasmic C-terminal tail domain that faces the nuclear pore complex and an N-terminal domain located in the perinuclear space. The C-terminal tail of gp210 consists of 58 amino acids while the luminal domain contains 1808 amino acids (including the signal sequence) with several N-linked oligosaccharides. Gp210 likely participates in the events that take place when a new nuclear pore complex is formed, as well as the transmission of signals from the perinuclear cisterna to the nuclear pore [44]. There are data to suggest that gp210 is organized into the

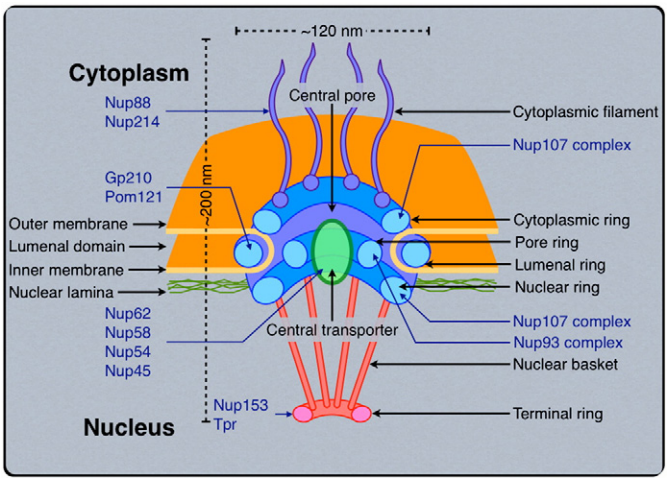

Fig. 1. Schematic diagram of a nuclear pore complex showing its major substructures and known localizations of several nucleoporins.