XENOBIOTIC INDUCED MODEL OF PRIMARY BILIARY CIRRHOSIS

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PRIMARNA BILIJARNA CIROZA INDUKOVANA KSENOBIOTIKOM: EKSPERIMENTALNI MODEL

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ABSTRACT

Primary biliary cirrhosis (PBC) is an autoimmune disease of the liver that is, characterised by destruction of the intrahepatic bile ducts and the presence of antimitochondrial antibodies (AMAs). Several murine models of PBC, with similar serological, biochemical, and histological features to human PBC, have been developed in recent years. These animal models enable investigators to study the etiology and pathophysiologic mechanism of PBC. Immune response in PBC is directed towards E2 components of the 2-oxo-acid dehydrogenase family of enzymes, which is in located in mitochondria and is an immunodominant epitope (a lipoylated peptide sequence shared by enzymes). Immunisation of mice with 2-octynoic acid coupled to bovine serum albumin (2-OA-BSA) (which is an antigen that is structurally related to the E2 subunit of the pyruvate dehydrogenase complex [PDC-E2]) produces histologic features similar to those found in human PBC. This model of xenobiotic induced PBC is suitable for studying the early events in PBC pathogenesis and for developing new therapeutics in PBC.

Key words: *PBC, xenobiotic, 2OA-BSA, C57BL/6 mice*

SAŽETAK

Primarna bilijarna ciroza (PBC) je autoimunska bolest jetre koju karakteriše destrukcija intrahepatičnih žučnih kanalića i prisistvo antimitohondrijalnih antitela (AMAs). Poslednjih godina je razvijeno nekoliko mišjih modela PBC koji imaju slične serološke, biohemijske i histološke karakteristike kao i humana PBC. Ovi animalni modeli su omogućili ispitivanje etiologije i mehanizama uključenih u patogenezu PBC. U PBC imunski odgovor je usmeren na E2 komponentu 2-okso-kiseline dehidrogenaza familije enzima koji su locirani u mitohondrijama, a imunodominantni epitop je peptidna sekvenca sa lipidima koja je zajednička za ove enzime. Imunizacija miševa 2-oktinoičnom kisleinom vezanom za goveđi serumski albumin (2-OA-BSA), antigenom koji je strukturno sličan E2 subjedinici kompleksa piruvat dehidrogenaze (PDC-E2), omogućava razvoj histoloških promena koje karakterišu PBC kod ljudi. Ovaj model PBC indukovan ksenobiotikom je pogodan za ispitivanje početnih događaja u patogenezi PBC i za razvoj novih lekova za PBC.

Ključne reči: *PBC, ksenobiotik, 2OA-BSA, C57BL/6 miševi*

INTRODUCTION

Primary biliary cirrhosis (PBC) is a liver-specific autoimmune disease (1). PBC has a long latency period, which is followed by the development of common symptoms: fatigue, pruritus hyperpigmentation, and (in the terminal stages) bleeding varices, and ascites (2). PBC is characterised by a multilineage humoral and cellular adaptive response against biliary epithelial cells (BECs) and destruction of small bile ducts by mechanisms that include innate immune responses (3; 4). Bile duct destruction leads to cholestasis, fibrosis, and ultimately liver cirrhosis (4). The typical characteristic of the disease is the presence of antimitochondrial autoantibodies (AMA), which are present in high amounts. The autoantigens to which the immune responese is directed in PBC has been identified as the E2 subunits of the 2-oxo-acid dehydrogenase complexes (2OADC-E2), including the E2 subunits of the pyruvate dehydrogenase complex (PDC-E2), branched chain 2-oxo acid dehydrogenase complex (BCOADC-E2), and 2-oxoglutarate dehydrogenase complex (OGDC-E2) (5). The immunodominant autoantigen within this group is PDC-E2 (6; 7). A multi-faceted immune response to the immunodominant mitochondrial autoantigen PDC-E2 in PBC

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