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The effects of DMARDs on the expression and function of P-gp, MRPs, BCRP in the treatment of autoimmune diseases

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ABSTRACT

The ATP-binding cassette (ABC) transporter family is a large class of ATP energy-dependent transmembrane proteins, and its primary function is to use the energy produced by ATP hydrolysis to transfer the substrate bound to the plasma membrane. This family is also closely related to multidrug resistance (MDR) in various diseases. Among the ABC transporter proteins, P-glycoprotein (P-gp), multidrug resistance-associated protein (MRP) and breast cancer resistance protein (BCRP) are the main members associated with MDR. At present, the roles of these transporters in therapeutic failures have been extensively studied and reviewed in cancer; however, they have rarely been described in autoimmune diseases (AIDs). AID is a group of chronic inflammatory diseases of unknown aetiology. AID's basic feature is the production of a large number of autoantibodies, which leads to extensive damage to multiple systems and multiple organs. Disease-modifying anti-rheumatic drugs (DMARDs) are commonly used in the treatment of AID, but a considerable number of patients have no response or develop resistance to these drugs over time. This phenomenon may be related to the abnormal expression of the ABC transporter, which leads to a decrease in the amount of drug entering cells that produce MDR. This article reviews the effects of DMARDs on the expression and function of P-gp, MRPs, and BCRP and the related molecular mechanism in the treatment of AID.

1. Introduction

AID is a group of chronic inflammatory diseases with unknown aetiology. In AID, T and B cells are over-activated, and they produce a large number of antibodies, resulting in extensive organ damage. Common AIDs include ulcerative colitis (UC) [1], rheumatoid arthritis (RA) [2], insulin-dependent diabetes mellitus [3], and systemic lupus erythematosus (SLE) [4]. Although the pathogenesis of AID has not been fully elucidated, for half a century a variety of hypotheses have been proposed to explain AID, such as genetic susceptibility and environmental factors triggering an abnormality immune response [5,6]. Presently, the treatment of AID is a challenge and a hotspot of research. Clinical routine drug therapy is still dominated by DMARDs and glucocorticoids. There are two main classes of DMARDs: biological (bDMARDs) and synthetic. Synthetic DMARDs can be further divided into targeted synthesis (tDMARDs) and conventional synthesis (sDMARDs) [7]. bDMARDs include etanercept, infliximab and so on [8]. tDMARDs include janus kinase (JAK) inhibitors, such as tofacitinib [9]. sDMARDs include methotrexate (MTX), sulfasalazine, cyclosporine A, leflunomide and so on [8]. sDMARDs are currently widely used in clinical practice. Notably, a large number of clinical studies have shown that nearly 80% of the traditional DMARDs are discontinued within two years, mainly because of reduced efficacy or toxicity [10,11]. Many scholars believe that the decline in drug efficacy may be related to drug resistance. A study by Morgan et al. showed that among 265 patients with RA, the rate of single drug resistance and MDR were 40% and 5%, respectively [12]. However, this resistance is closely related to certain ABC transporters.

2. ABC transporter proteins

The ABC transporter family, a large class of transmembrane proteins, has very characteristic structures that contain a full transporter or semi-transporter. The whole transporter contains two transmembrane domains (TMD) and two nucleotide binding domains (NBD) as well as semi-transporters containing only one TMD and one NBD [13–15] (see Fig. 1). Its primary function is to use the energy generated by ATP hydrolysis to transfer the substrate to which it binds to the plasma membrane [14]. According to the homology of the conserved region sequence, ABC transporters can be divided into 7 subtypes

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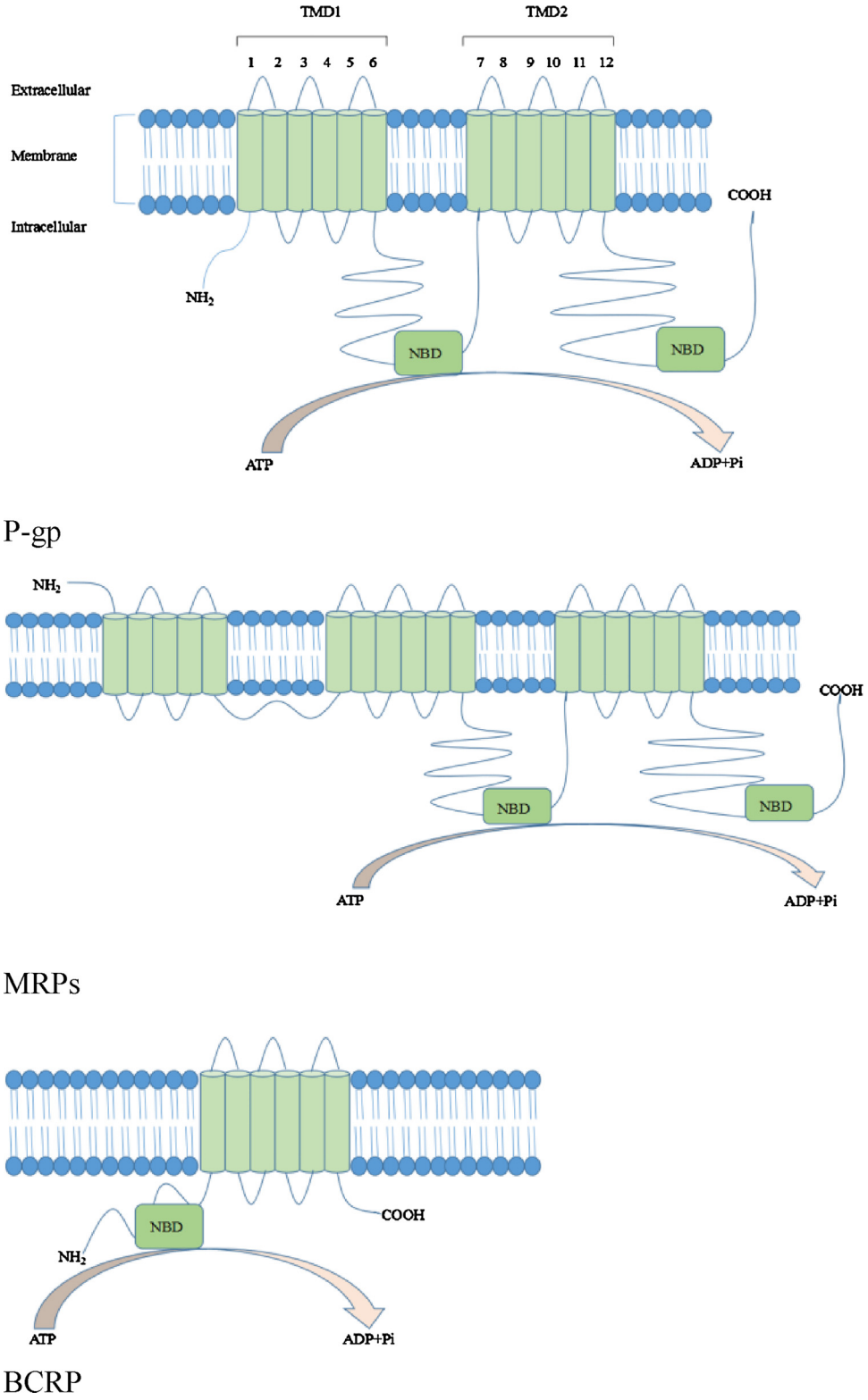

Fig. 1. Predictive secondary structure of the ABC family drug transporter vector. TMD (transmembrane domains); NBD (nucleotide binding domains).

(ABCA–ABCG) [16,17]. Among them, P-gp (ABCB1), MRP (ABCC), and BCRP (ABCG2) have been reported relatively widely [18,19].

2.1. P-gp

P-gp is a transmembrane glycoprotein with a molecular weight of 170 kD. It was first described by Juliano and Ling in 1976 [20]. P-gp is a product of the MDR1 gene, which comprises 2 monomers. Each monomer comprises 1280 amino acids, 6 transmembrane regions and 1 adenosine triphosphate (ATP) binding site [21,22]. P-gp is a transmembrane drug efflux pump that relies on ATP hydrolysis energy to pump hydrophobic lipophilic drugs out of the cell and maintain the intracellular drug concentration at a low level [23–29] (see Fig. 2). P-gp is usually expressed or induced in a variety of tissues and cells, such as