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Invited review

MRP4 (ABCC4) as a potential pharmacologic target for cardiovascular disease

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ABSTRACT

This review focuses on multidrug resistance protein 4 (MRP4 or ABCC4) that has recently been shown to play a role in cAMP homeostasis, a key-pathway in vascular biology and in platelet functions.

In vascular system, recent data provide evidence that inhibition of MRP4 prevents human coronary artery smooth muscle cell proliferation *in vitro* and *in vivo*, as well as human pulmonary artery smooth muscle cell proliferation *in vitro* and pulmonary hypertension in mice *in vivo*.

In the heart, MRP4 silencing in adult rat ventricular myocytes results in an increase in intracellular cAMP levels leading to enhanced cardiomyocyte contractility. However, a prolonged inhibition of MRP4 can promote cardiac hypertrophy. In addition, secreted cAMP, through its metabolite adenosine, prevents adrenergically induced cardiac hypertrophy and fibrosis.

Finally, MRP4 inhibition in platelets induces a moderate thrombopathy. The localization of MRP4 underlines the emerging concept of cAMP compartmentalization in platelets, which is a major regulatory mechanism in other cells. cAMP storage in platelet dense granules might limit the cAMP cytosolic concentration upon adenylate cyclase activation, a necessary step to induce platelet activation.

In this review, we discuss the therapeutic potential of direct pharmacological inhibition of MRP4 in atherothrombotic disease, *via* its vasodilating and antiplatelet effects.

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Contents

Abbreviations: ABC, ATP-binding cassette; AC, adenylate cyclase; AKAP, A-kinase anchoring protein; AR, adenosine receptor; CABG, coronary artery bypass graft; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; COX, cyclooxygenase; δ-SPD, δ-storage pool deficiency; MRP, multidrug resistance protein; MSD, membrane-spanning domain; NBD, nucleotide-binding domain; NO, nitric oxide; PDE, phosphodiesterase; PGI_2, prostaglandin I2; PKA, protein kinase A; PKG, protein kinase G; sGC, soluble guanylate cyclase; SMC, smooth muscle cell; TXA2, thromboxane A2; VASP, vasodilator-stimulated phosphoprotein.

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1. Introduction

The multidrug resistance proteins (MRPs) belong to a family of transmembrane proteins using the energy produced by ATP hydrolysis to pump diverse endogenous compounds and xenobiotics out of various cells. Among them, MRP4 (or ABCC4) is capable of pumping cyclic nucleotides that control multiple cardiovascular processes, including cardiac hypertrophy, cardiac contractility, myocardial fibrosis, endothelial barrier function, vascular smooth muscle cell proliferation and vasodilation. On the other side, cyclic nucleotide homeostasis is essential to maintain platelets in an inactive state to avoid inappropriate activation and clot formation. Although the major role of cAMP in platelet regulation has been known for years, the underlying molecular mechanisms are only beginning to emerge.

In this review, we report recent data providing an active role for MRP4 in the efflux of cAMP by various cell types, notably smooth muscle cells and cardiomyocytes. Moreover, we describe MRP4 as a new player for the compartmentalization of cAMP in platelet dense granules.

2. Multidrug resistant protein-4

ABC (ATP-binding cassette) transporters are a super-family of transmembrane proteins that use the energy produced by ATP hydrolysis to pump out a variety of endogenous molecules as well as xenobiotics. The ABC transporters contain four domains: two membrane-spanning domains (MSDs), each containing six transmembrane helices, and two cytoplasmic nucleotide-binding domains (NBDs) (Fig. 1). The NBDs contain Walker A and B motifs and a LSGGQ motif, which is specific of ABC transporters. Walker domains are involved in the binding and hydrolysis of two ATP molecules. The members of the ABCC sub-family were formerly known as multidrug resistance proteins (MRPs), given their ability to extrude anticancer drugs from cells. Some ABCC transporters have an NH2-terminal extension with an extracellular N-terminus, a third membrane spanning domain (MSD0) and an intracellular loop (L0) and therefore are considered as "long" MRPs.

Different models have been proposed to explain the mechanism of action of ABC, the more recent considering that a continuous sequence of ATP binding and hydrolysis into ADP is necessary to induce a conformational change necessary for substrate binding and its subsequent efflux [1,2]. This model so-called "Constant Contact Model" proposes that both NBD domains are constantly in contact with an adenine nucleotide in its ATP or ADP form. The hydrolysis cycle consists in the ATP hydrolysis into ADP on the first NBD domain, quickly followed by its substitution by a new ATP molecule. The binding of this new ATP molecule induces changes in the transporter conformation that modify the affinity for its substrate. The hydrolysis of ATP alternatively occurs on NBD 1 or NBD 2 domains, allowing either entrance or release of the substrate by the transporter [1,2].

Among the MRP family, MRP4 (ABCC4) is one of the most characterized "short" ABCCs. *ABCC4* gene located on chromosome 13q32.1 is highly polymorphic and, consecutively to an alternative splicing, leads to 3 MRP4 isoforms, isoform 1 being the most important. To date, no genetic disease has been linked to altered MRP4 function [3]. MRP4 is present in a large variety of cells, although weakly expressed. By contrast with the other members of ABCC subfamily, MRP4 has the particularity to be localized either to the apical or to the basolateral membrane of polarized cells. It has been involved in the active transport of various drugs, mainly nucleoside analogues, antibiotic and antineoplastic agents, and signaling molecules. Therefore, its physiological role includes elimination of drugs and endogenous molecules. In some pathophysiologi-

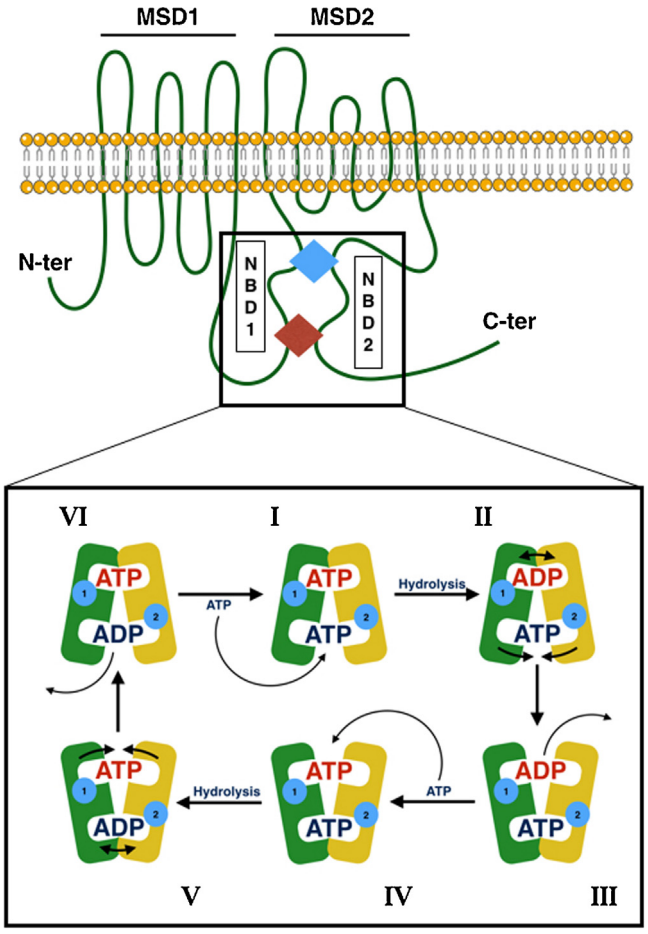

Fig. 1. Topology and hypothetical transport cycle of MRP4.
The upper panel is a schematic representation of MRP4 topology, composed of 2 membrane spanning domains (MSD). Each MSD contains 6 transmembrane helices and a nucleotide binding domain (NBD). NBDs consist essentially in 2 walker motifs, Walker A and Walker B (red and blue diamonds). NBDs are positioned in head to tail leading to association of Walker A of NBD1 with the Walker B of the NBD2, and conversely. The lower panel represents the latest hypothetical model of transport cycle called "constant contact", suggested by Sauna et al. [1]. Step I is an asymmetric occluded nucleotide conformation. Only ATP occluded at the site 1 is hydrolyzed into ADP (Step II). Formation of ADP leads to the dissociation of the two NBD and the release of formed ADP (Step III). An ATP is immediately bound at the free site, but not occluded (Step IV). Conversely, ATP on the site 2 is occluded and then hydrolyzed into ADP (Step V), which is subsequently released (Step VI) and replaced by an ATP, while ATP on the site 1 is once again occluded to complete the cycle.

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