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Review

Current advances on ABC drug transporters in fish

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ABSTRACT

Most members of the large ATP-binding cassette (ABC) gene family are transporters involved in substrate translocation across biological membranes. In eukaryotes, ABC proteins functioning as drug transporters are located in the plasma membrane and mediate the cellular efflux of a wide range of organic chemicals, with some transporters also transporting certain metals. As the enhanced expression of ABC drug transporters can confer multidrug resistance (MDR) to cancers and multixenobiotic resistance (MXR) to organisms from polluted habitats, these ABC family members are also referred to as MDR or MXR proteins. In mammals, ABC drug transporters show predominant expression in tissues involved in excretion or constituting internal or external body boundaries, where they facilitate the excretion of chemicals and their metabolites, and limit chemical uptake and penetration into "sanctuary" sites of the body. Available knowledge about ABC proteins is still limited in teleost fish, a large vertebrate group of high ecological and economic importance. Using transport activity measurements and immunochemical approaches, early studies demonstrated similarities in the tissue distribution of ABC drug transporters between teleosts and mammals, suggesting conserved roles of the transporters in the biochemical defence against toxicants. Recently, the availability of teleost genome assemblies has stimulated studies of the ABC family in this taxon. This review summarises the current knowledge regarding the genetics, functional properties, physiological function, and ecotoxicological relevance of teleostean ABC transporters. The available literature is reviewed with emphasis on recent studies addressing the tissue distribution, substrate spectrum, regulation, physiological function and phylogenetic origin of teleostean ABC transporters.

Contents

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1. Introduction

When considering the interaction of organisms with the surrounding chemosphere, central questions regard the mechanisms of chemical uptake and elimination, as well as that of chemical distribution between different body compartments (Van Aubel et al., 2002). It is well documented that biotransformation crucially affects chemical fate in fish (Schlenk et al., 2008). In contrast, the impact of active transport across cellular membranes on chemical fate is still incompletely understood in teleosts. While such transport mechanisms likely affect bioaccumulation and toxicity of pollutants in fish (Nichols et al., 2007), an understanding of the specific interactions of environmental chemicals with transport proteins and the ecotoxicological relevance of such interactions is currently only beginning to emerge.

In eukaryotes, ABC (ATP-binding cassette) proteins comprise an important group of transporters that control the movement of compounds between the external environment and the internal milieu, and between body compartments. These proteins were first described as biochemical factors conferring multidrug resistance (MDR) in cancer, i.e., the resistance of tumour cells against structurally and functionally unrelated cytostatic drugs (Roninson et al., 1984; Gros et al., 1986). These MDR conferring proteins are localised in the cell membrane and function as ATP-dependent biochemical pumps mediating the cellular efflux of a diverse array of organic chemicals and some metals (Gottesman et al., 2002). ABC drug transporters also show high expression levels in normal tissues involved in excretion (e. g., kidney, liver) or acting as barriers (gut epithelium, capillary endothelia forming the blood–brain barrier) (Fojo et al., 1987; Thiebaut et al., 1987). ABC drug transporters often localise to the apical side of polarised epithelial cells, suggesting their role in limiting chemical uptake and enhancing chemical elimination, thus contributing to the biochemical defence against toxicants (Leslie et al., 2005). In support of such a role, animals lacking certain ABC drug transporters as the result of natural or targeted mutations usually are healthy and viable, but can show marked hypersensitivity to specific toxicants or mild pathophysiological changes reflecting the impaired excretion of endogenous toxicants (Schinkel et al., 1994, 1995; Wijnholds et al., 1997; Kruh et al., 2007; Lagas et al., 2009). Kurelec and co-workers were the first to report the induction of ABC transporters in marine invertebrate populations from polluted habitats (Kurelec and Pivcevic, 1991; Kurelec et al., 1995). In analogy to the phenomenon of MDR in cancer cells, Kurelec and colleagues coined the term "multixenobiotic resistance (MXR) proteins" for ABC drug efflux transporters in aquatic animals, reflecting the role of the cellular pumps as protective factors against pollutant toxicity (Kurelec and Pivčević, 1989; Kurelec and Pivcevic, 1991; Kurelec, 1992). While the term "MXR proteins" is well established in aquatic toxicology, the present review will employ the more general term "ABC drug transporters" in order to avoid using different terminologies when referring to aquatic and terrestrial animal models.

First evidence for the ABC drug transporter Abcb1[1] (P-glycoprotein) in teleost was provided by a molecular genetic study in winter flounder (*Pleuronectes americanus*) (Chan, 1992). The presence of Abcb1-like proteins in fish was subsequently confirmed in an immunohistochemical study in guppy (*Poecilia reticulata*) (Hemmer et al., 1995). Moreover, P-glycoprotein-like transport activities were measured in isolated proximal tubules from winter flounder and killifish (*Fundulus heteroclitus*) (Miller, 1995; Schramm et al., 1995; Sussman-Turner and Renfro, 1995). Subsequently, ABC drug transporters have been studied in a number of tissues of different teleosts, using immunochemical detection (Hemmer et al., 1998; Cooper et al., 1999; Kleinow et al., 2000; Albertus and Laine, 2001) and transport assays (Doi et al., 2001; Sturm et al., 2001b; Miller et al., 2002). Recently, cDNA sequences have been obtained for various ABC drug transporters (Zaja et al., 2008b; Paetzold et al., 2009; Fischer et al., 2010, 2011, 2013; Loncar et al., 2010; Popovic et al., 2010; Sauerborn Klobučar et al., 2010; Costa et al., 2012; Diaz de Cerio et al., 2012), and the ABC gene family has been annotated and analysed phylogenetically in zebrafish (*Danio rerio*) and channel catfish (*Ictalurus punctatus*) (Annilo et al., 2006; Liu et al., 2013). Moreover, a teleost cell line showing enhanced expression of a specific teleost ABC drug transporter has been generated, which enables the identification of environmentally relevant compounds that interact with this efflux pump (Caminada et al., 2008; Zaja et al., 2008a, 2011; Smital et al., 2011).

The aim of the present review article is to summarise recent insights into ABC transporters in teleost fish, focusing on data that have become available since earlier reviews on the subject (Bard, 2000; Sturm and Segner, 2005). Molecular, physiological and in vitro studies on ABC transporters are reviewed focusing on teleosts, but also taking into account studies on elasmobranchs where available. Since the annotation of ABC drug transporters in zebrafish (Annilo et al., 2006), genome assemblies have become available in further teleost species, allowing to draw a more complete picture of the complement of ABC drug transporters present in this economically and ecologically important vertebrate taxon. To this end, evolutionary relationships between ABC drug efflux transporters from selected tetrapods and the presently seven teleost species with available genome assemblies are presented.

1.1. Teleosts and other fishes

"Fish" have been defined as aquatic vertebrates having gills and fin-shaped limbs (Nelson, 2006). This definition comprises more than half of the extant vertebrates, and includes taxa as diverse as jawless (Agnatha), cartilaginous (Chondrichthyes) and bony fishes (Osteichthyes) (Helfman et al., 2009). The first fossil evidence for the Chondrichthyes, which include the elasmobranchs (sharks and rays), dates from the early Devonian (418 mya). Osteichthyes are divided

[1] Our designation of gene and protein names is based on the Zebrafish Nomenclature Guidelines (http://zfin.org/zfinfo/nomen.html); fish: *shh*/Shh, human: *SHH*/SHH, mouse: *Shh*/SHH (gene/protein).