

ATP-binding cassette (ABC) transporters as emerging targets in modulation of neural stem cells behavior in neurodegenerative diseases and cell therapy benefits

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Abstract

Increasing incidence of central nervous system (CNS) disorders has become a major challenge for both basic and clinical scientific society to develop novel therapeutic models for treatment. The knowledge of stem cells has added a new dimension in the research towards finding more appropriate targets responsible for the disease fate determination. As stem cell research is progressing day by day in routine research laboratories there is great hope to find suitable therapeutic targets for complete cure of the CNS disorders. Discovery of ABC transporters in animal tissues has emerged as new spot for several disease prognosis and therapeutic target. ABC transporters are membrane proteins expressed in various organs like liver, kidney, blood-brain barrier, blood-testis barrier etc. It is involved in various important cellular processes such as absorption, distribution and excretion of drugs, xenobiotics and endogenous compounds showing their role in tissue defense and organ regeneration. The current review explains about the role of ABC transporters in CNS pathogenesis and defense adding stem cells therapeutic strategies.

Keywords: ABC transporters; Neurodegenerative diseases; Stem cell therapy

Introduction

ABC transporters are ATP-dependent membrane proteins which are expressed in a variety of organs, such as the kidney, liver, placenta, intestine, blood-testes barrier and blood-brain barrier. In these organs ABC transporters and its members play vital role in many cellular processes such as absorption, distribution, and excretion of various types of drugs, toxins, xenobiotics, and endogenous compounds (Fig. 1). Based on the sequence homology, order of domain and similarity in gene structures 49 members of human ABC transporters have been identified and are divided into seven subfamilies from A to G. Although few ABC transporters have been studied comprehensively in bacteria, yeast and other organisms, the functional annotation of many others are still need to identify. Mostly identified ABC transporters have two types of primary structures 1) full transporters and 2) half transporters. Each have different way of interactions with the molecules and are most important component in defense mechanisms (Fig. 2). With the disease perspectives 16 ABC genes have been identified linked to inherited diseases, such as Tangier disease (ABCA1), Dubin Johnson

syndrome (ABCC2), *pseudoxanthoma elasticum* (ABCC6), and cystic fibrosis (ABCC7) (Dean, 2005). Development of Knockout animal models for ABC transporters has provided us with some insights into the function and characteristics of ABC transporters (Schinkel et al., 1997; Xia et al., 2007; Glaeser and Fromm, 2008). The knowledge of neural stem cells (NSCs) has added a new dimension for the study of CNS regeneration based on cellular and molecular depiction. However, a variety of molecular targets are being identified involved in CNS damage and regeneration, none of them have proved their potential as appropriate prognostic and therapeutic targets. Hence, there is need to identify more appropriate molecular switches that is responsible for specific disease condition and can be targeted to improve the cell therapy benefits. In this scenario targeting the molecular pathways involved in NSCs proliferation and differentiation would probably help to identify the defined target for CNS regeneration.

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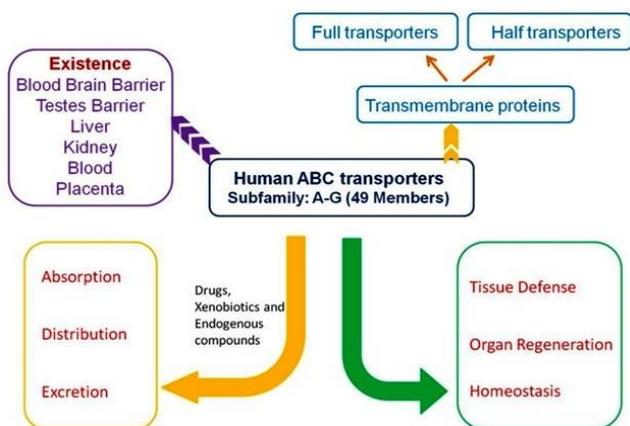


Fig 1 Schematic representation of human ABC transporters existence and their role in tissue defense and organ regeneration by excretion, absorption and distribution of toxic substances within/out of the cells.

NSCs are specialized cell populations within the central nervous system (CNS) tissue and characterized as self-renewing and multipotent in nature having capacity to generate neurons and glia upon differentiation. They can be isolated, genetically manipulated and differentiated in vitro retaining its ability to reintroduce in cell replacement therapies for the treatment of various neurodegenerative diseases. During differentiation characterization of genes with tightly controlled expression patterns signifies extensive approach to understand the regulatory behavior of stem cells.

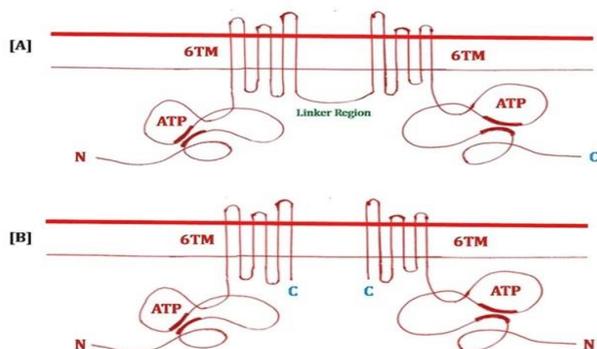


Fig 2: Two primary types of membrane associated ABC transporter proteins [A] Full transporter shows mirror image halves separated by a flexible linker region essential for catalytic activity. Each half of the molecule is a 6-transmembrane spanning domain (6TM) that blocks the transporter proteins to the plasma membrane [B] Half transporters are consist of only one halve and require membrane association with other half transporter to form the pure complex. There is no linker region present in the half transporter proteins.

The regulation of NSCs behavior in vitro and in vivo by using ABC transporters has emerged an essential innovative meadow of investigation as major focus on their integrated analysis in NSCs proliferation, differentiation and regulation, along

with comparison to that in hematopoietic and other stem cells (To Kenneth et al., 2011; Ishimoto et al., 2014).

ABC transporters and stem cells

Stem cells have become a major target of interest for identifying molecules with tightly controlled expression during proliferation and differentiation in order to get more suitable molecular target to understand the disease pathogenesis and tissue defense mechanisms (Fig. 3). In this perspective, ABC transporters represent a strong applicant to be studied in more comprehensive way to understand their role in stem cells proliferation and differentiation. Discovery of P-gp on CD34 positive hematopoietic cells by Chaudhari and Roninson (1991) emerged a new insight for separate category of molecule to study in disease perspectives. Ten years later, expression and functional activity of BCRP in these cells was identified by Zhou et al., (2001). They are normally characterized by their low retention of rhodamine 123, transported by P-gp or BCRP (Litman et al., 2000; Honjo et al., 2001), and Hoechst dye 33342, transported by BCRP in the cells and termed as side population (SP) cells (Golebiewska et al., 2011).

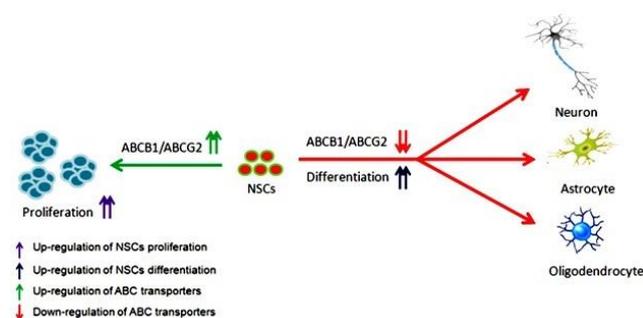


Fig 3: Role of ABC transporters in NSCs proliferation and differentiation. Usually during NSCs proliferation expression of ABC transporters increases and decreases during differentiation

Now, it is well known that the SP population cells are not only resides within the bone marrow but also in other nonhematopoietical organs, such as umbilical cord blood, brain, spleen tissue, kidney, heart, skin, intestine, and lungs (Asakura and Rudnicki, 2002; Yano et al., 2005; Larderet et al., 2006). In these organs, they have ability to differentiate into several cell types following re-introduction in vivo, including neurons, cardiac and skeletal muscles, and epithelial cells like hepatocytes (Ferrari et al., 1998; Alison et al., 2000; Lagasse et al., 2000; Mezey et al., 2000; Krause et al., 2001; Jackson et al., 2001).

ABC transporters in tissue defense and organ regeneration

Various studies have demonstrated the significant role of various ABC transporters in tissue defense through the excretion of toxic compounds and their metabolites (Russel et al., 2002; Szaka'cs et al., 2008). The transporters are expressed in highly controlled manner, emphasizing their consequences in organ protection (Leslie et al., 2005). Two most studied ABC transporters, the multidrug resistance gene 1 product (MDR1/ABCB1), P-glycoprotein (P-gp), and ABCG2 or breast cancer resistance protein 1 (BCRP), have been found to be implicated in tissue regeneration (Padmanabhan et al., 2012). Both the efflux pumps are highly expressed on side population (SP) cells in a variety of tissues. Loss of expression for transporter genes leads to cell differentiation, indicating that they might determine stem cell-induced tissue remodeling through their differential expression. SP cells have been demonstrated for their implication in organ regeneration (Jackson et al., 1999; Lagasse et al., 2000; Jackson et al., 2001).

The localization of ABC transporters within the organ with a barrier function, and the broad substrate specificities imply their role in tissue defense. In brain drug distribution is hampered by few ABC transporters like P-gp, multidrug resistance proteins 1 and 2 (MRP1/2; ABCC1/2), MRP4 (ABCC4), and BCRP in the blood-brain barrier (Kusuhara and Sugiyama, 2001; Begley, 2004; Perriere et al., 2007). The defense mechanism formed by ABC transporters under physiological conditions is intended against accumulation of potentially harmful compounds. Interestingly, during organ damage or disease conditions, changes in the gene expression levels of ABC transporters have been observed, probably to balance for the increased consignment of detrimental products of oxidative stress formed during an insult or to compensate for the loss of efflux pumps in damaged tissues (Mangum et al., 2011; Abdullah et al., 2013).

ABC transporters in human neurodegenerative diseases

In 1976, when Drs. Juliano and Ling reported the overexpression of membrane proteins in colchicine-resistant Chinese hamster ovary cells they found the acquired resistance to many structurally unrelated antineoplastic drugs. The over expressed membrane protein was later determined to be a member of ABC transporter superfamily. The ABC domains of these proteins hydrolyze ATP, providing energy for transport of various substrates

across the membrane against a high concentration gradient.

Now most highlighted issues of current pharmaceutical biotechnology and cell therapy contains several reviews that summarize the role of the ABC transporters in cellular and molecular therapy as well as in protecting healthy tissue from the xenobiotics and other toxic compounds by modulating various transcription factors and genes. Robey et al. (2001) demonstrated the clinical interventions with ABCG2. Two in-depth articles on the latest important developments in utilizing therapeutic strategies to overcome ABC transporter-mediated drug resistance are reviewed by C-P. Wu et al. 2008 (Natural product modulators of ABC drug transporters) and Stolarczyk et al. 2011 (Targeting phosphorylation to regulate ABC transporter function).

Another important pharmacological / physiological function of ABC transporters is to provide protection by effluxing xenobiotics (including drugs used to treat diseases) from tissues including kidney, testes, brain, and developing human fetus. Hartz and. Bauer (2010) summarized the recent findings on ABC transporter regulation in the CNS especially at the blood-brain barrier and discuss the role of ABC transporters in CNS diseases, including seizures, epilepsy, brain cancer, and alzheimer's disease. Another study by Ni and Mao (2011) provided a thorough discussion of the protective roles of ABC transporters in the placenta that attenuates toxicity in the developing fetus.

ABC transporters and stem cell therapeutic approaches for human neurodegenerative disorders—how to make it work

ABC transporters play a crucial role in several physiological barriers such as the blood brain barrier, blood-cerebrospinal fluid (B-CSF) barrier, and blood-testis barrier modulating the absorption and excretion of xenobiotics across these barriers. Within the CNS, these transporters are localized at the luminal membrane of endothelial cells of blood capillaries where they actively modulate the permeation of xenobiotics. The over-expression of several transporters has been observed in various types of tumors causing multidrug resistance (MDR) to treatment with chemotherapeutic agents (Gangavarapu et al., 2013). Moreover, resistance to CNS drugs, such as antidepressant, antiepileptic and anti-HIV medicine, may also be related to over expression of ABC transporters. Recently, it has been reported that alterations in ABC expression and function are related to the etiology and pathogenesis of neurologic disorders, such as alzheimer's disease and parkinson's disease.

However, a recent study reported that ABC expression and function are strongly decreased during the neuro-inflammation process in multiple sclerosis and neuroblastoma (Ingram et al., 2013).

Recent progresses in stem cell biology and therapeutic interventions there is a hope to get the cellular therapies for several human neurodegenerative diseases (Solomon et al., 2012). However, before initiation of their use in clinical trials, we should be able to control stem cell proliferation and differentiation into specific cell phenotype, proper induction of their integration into existing neural and synaptic circuits, and optimized functional recovery in animal models closely resembling to the human diseases.

Recent and future challenges for cellular therapeutic benefits

As with any new medical intrusion, development of stem-cell therapies must awe the scientific and ethical guidelines of human testing. There is need to answer the following questions before claiming the triumph in using stem cells to treat neurodegenerative diseases:

- Types of stem cells used in different diseases.
- Suitable route for stem cells delivery to make functional acquaintances with the host cells.
- Safety and efficacy of stem cells delivery into people with debilitating diseases.
- Applicability of immunosuppressive drugs to prevent the immune rejection of implanted cells.
- Toxic effects and tolerable ability of the patients against these drugs.
- Potential long-term complications of stem-cell therapies.
- Migration of transplanted cells to its original niche of damaged tissue.
- Tumor development.
- Progression of the disease condition, functional improvements, or speed recovery for patients with diseases.
- Modulation of stem cells transcription factors and other proteins playing significant roles in stem cells proliferation and differentiation.

It is an exciting time, but we must move forward with meticulous regard for the scientific process and cautious respect for what we do not know and can't anticipate. The answers to the myriad questions are needed to be addressed. With the guidance and assistance of regulatory agencies, scientists and clinicians from different areas must work together to make this hope a reality.

Next steps toward cell therapy and repair

Further research is needed in order to prove its ability to coax endogenous stem cells in the adult nervous system to respond in better way to the injury. It will also provide the acceptable cells for transplantation after modifying gene expression patterns further to ameliorate different types of diseases. The types of nervous system diseases that represent the best targets for stem cell-based therapies are those that would be improved by the transplant or induced replacement of a limited number of cell types. Sensory disorders, parkinson's and glial diseases fall into this category and could potentially be cured by a cell-replacement therapy by modifying the expression of ABC transporters and HSPs. Motor system disorders and spinal cord injuries are more complex, but given their severity and lack of current treatment options, it can be argued that any improvement in function would be of great benefit. Drug transporters and HSPs expression analysis by various studies have demonstrated their role in such diseases and may provide a better target to settle the treatment strategies (Schumacher et al., 2012; Zheng et al., 2013; Alberto et al., 2014).

The hope of using stem cells to intervene in neurodegenerative disease is promising, but due to various complexities of the central nervous system, advancements will likely continue in deliberate steps. Further to move the research forward, it is critical to measure the efficacy of any experiment involving human and animal subjects. Despite the molecular differences between neurodegenerative diseases, their eventual stem cell therapies will likely share many features such as information gained in one field can drive forward progress in the others.

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Conflict of interest

The authors declare no conflict of interest

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