Cell Biology: Research and Therapy

Review Article A SCITECHNOL JOURNAL

Are Channels Fundamentally Different from Transporters? Evaluating CFTR as a Specific Example

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Received date: 06 June, 2022, Manuscript No. CBRT-22-67798;
Editor assigned date: 09 June, 2022, PreQC No. CBRT-22-67798 (PQ);
Reviewed date: 23 June, 2022, QC No. CBRT-22-67798;
Revised date: 29 August, 2022, Manuscript No. CBRT-22-67798 (R);
Published date: 07 September, 2022, DOI: 10.4172/2324-9293.1000165.

Abstract

In this article, we want to show whether there are differences between channels and transporters and whether the channel and the transporter may be assumed to be in the same category. Certain proteins, such as Cystic Membrane Transduction Regulator (CFTR), seem to challenge our understanding of the concept of channel and transporter. Studies have shown that the concentration of chlorine outside the cell is normally higher, but due to the operation of channels, especially ENaC, the concentration of chlorine inside the cell increases and in order to continue these processes, it must be transferred outside the cell. We finally conclude that CFTR may be a transporter.

Keywords: Chlorine channel; Carrier; ABC family

Introduction

There are two types of proteins in the membrane which carry substances: Channels and transporters [1]. These proteins are responsible for transporting substances through the membrane but are structurally and functionally different [2]. The channels have some important characteristics:

- Only certain types of substances are allowed to pass like transporters.
- Many channels have gates for opening and closing which are regulated by electrical signals (voltage-gated channels) or chemicals that bind the channel proteins (ligand-gated channels) or mechanical stimulation (mechanosensitive ion channels) [3].
- Channels transport substances down their electrochemical gradient.
- Channels usually have permanent pores (Some of them have gates and some do not).
- The speed of substances passing in channels is higher.

The second protein in the membrane which carries substances is transporter. Transporters have also some important characteristics:

- Transporters pass substances down their electrochemical gradient which is called “passive transports”.
- Transporters pass substances against their electrochemical gradient which is called “active transport”.
- Transporter does not have gates and has temporary pore and special structures which allow substances to pass through by changing their shape.
- The speed of substances passing in transporters is lower than channels.

Literature Review

In this article we want to know whether there are differences between channels and transporters or not? And whether the channel and the transporter can be assumed to be in the same category? Certain proteins, such as Cystic Membrane Transduction Regulator (CFTR), seem to challenge our understanding of the concept of channel and transporter.

CFTR is a membrane transport protein and chloride channel which belongs to the ABC (ATP binding cassette) family. ABC transporter is an integral membrane protein that is responsible for the ATP transport of many substrates across membranes [4]. Most members of this family are pumps except CFTR. CFTR acts as a unique member of the ABCs family not only as a pump, but also as a channel [5]. However, some articles also emphasize that CFTR is a pump. While other ABC transporters pass substances by the chemical energy of ATP hydrolysis based on their chemical gradient, CFTR leads anions down their electrochemical gradient (Table 1) [6].

Article name	Pore	ATP consumption	Concentration gradient	Channel/Transporter
Rees DC, Johnson E and Lewinson O. ABC transporters: the power to change.		+		Channel
Muallem D and Vergani P. ATP hydrolysis-driven gating in cysticfibrosistrans-membrane conductance regulator.	+	+		Channel

Miller C. CFTR: break a pump, make a channel.		+		Transporter
Linsdell P. Cystic Fibrosis Trans-membrane conductance Regulator (CFTR): Making an ion channel out of an active transporter structure.	+	+		Channel
Linsdell P. Functional architecture of the CFTR chloride channel.	+	+	Down their electrochemical gradient	Channel
Liu F, Zhang Z, Csanády L, Gadsby DC and Chen J. Molecular structure of the human CFTR ion channel.		+	Down their electrochemical gradient	Channel
Csanády L, Vergani P and Gadsby DC. Structure, gating, and regulation of the CFTR anion channel.	+	+		Channel
Gadsby DC, Vergani P and Csanády L. The ABC protein turned chloride channel whose failure causes cystic fibrosis.	+	+	Either direction	Channel
Hwang TC and Kirk KL. The CFTR ion channel: gating, regulation, and anion permeation.	+	+	Down their electrochemical gradient	Channel
Csanády L, Nairn AC and Gadsby DC. Thermodynamics of CFTR channel gating: a spreading conformational change initiates an irreversible gating cycle.		+		Channel
Farkas B, Tordai H, Padányi R, Tordai A, Gera J, Paragi G and Hegedűs T. Discovering the chloride pathway in the CFTR channel.	+	+	Down their electrochemical gradient	Channel
Hwang TC, Yeh JT, Zhang J, Yu YC, Yeh HI, and Destefano S. Structural mechanisms of CFTR function and dysfunction.	+	+	Down their electrochemical gradient	Channel
Saint-Criq V and Gray MA. Role of CFTR in epithelial physiology.		+	Down their electrochemical gradient	Channel

Table 1: Checking whether CFTR is a transporter or channel based on the information in various articles.

Discussion

CFTR protein plays an important role in regulating the secretion and absorption in epithelial cells in the respiratory tract (especially pulmonary ionocytes), gastrointestinal tract, reproductive tract, sweat, and salivary glands that regulate many mechanisms such as maintaining hydration on the surface of these cells. This protein is said to be an AT Pgated channel found in epithelial cells and is responsible for transmitting Cl^- and HCO_3^- [7]. This protein has two membrane domains (TMDs; TM1-TM6 in TMD1 and TM7-TM12 in TMD2), each followed by two cytoplasmic NBDs (NBD1 and NBD2) [8]. It also has a Regulatory domain (R) with multiple phosphorylation sites. Activation of this protein typically requires R-domain phosphorylation by the protein kinases PKA and PKC; however, the interaction between ATP and NBDs are required for gating [9]. It is said that the open state of this protein is when it is open inside the cell and the closed state is when it is out of the cell [10]. NBD subunits are ligand binding sites which typically open the CFTR gateway when ATP attaches to this site at each NBD and it is consumed during the gating cycle. As stated in the channel definition, no channel uses energy to transport substances, but ATP is involved in the function of this protein that is based on this hypothesis, thus, it can be said that CFTR

acts as a pump [11,12]. There are currently two theories in the articles for ATP activity in CFTR:

- As mentioned, if ATP is consumed in the gating cycle, then why does CFTR pass the substances down their electromechanical gradient? If the substances pass down their electrochemical gradient and uses ATP energy simultaneously, it is known as a transporter, not a channel.
- According to researches, the activity of this protein is dependent on the phosphorylation of the R domain by cAMP dependent Protein kinase A (PKA) and its ATPase activity. Phosphorylation requires the operation of Nucleotide Binding Domain (NBD) subunits. These domains bind to the chemical energy molecule ATP and have an ATP binding site where ATP hydrolysis occurs. When ATP does bind, these two NBDs associate to form a dimer and the pore in CFTR opens. These subunits have an ATP binding site where ATP hydrolysis occurs. Hydrolysis of ATP is approximately 90% involved in phosphorylation and 10% in the enzymatic activity of this protein. According to experiments, phosphorylation does not occur if ATP hydrolysis defects, although the protein is still conductive. Therefore, it can be concluded that phosphorylation is dependent on the hydrolysis of ATP.

Conclusion

As shown in the Table above, many articles state that CFTR is a channel. However, it can be said that CFTR is also a transporter. Studies have shown that the concentration of chlorine outside the cell is normally higher, but due to the operation of channels, especially ENaC, the concentration of chlorine inside the cell increases and in order to continue these processes, it must be transferred outside the cell (In CF disease when CFTR is not working properly, the concentration of chlorine and sodium in the cell increases). On the other hand, some scientists confirm that CFTR has a pore and some others believe that this pore is defective and that is why this protein is called a broken pump.

Conflict of Interest

There is no conflict of interest in this research.

Ethical Approval

This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Ravna AW, Sylte I (2011) Homology modeling of transporter proteins (carriers and ion channels). Homolog Model 857:281-299.
2. Hall JE, Hall ME (2020) Guyton and Hall textbook of medical physiology e-Book. 14th edition, Elsevier Health Sciences, Philadeiphia, Canada, 1150.
3. Reece JB, Urry LA, Cain ML, Wasserman SA, Minorsky PV, et al. (2014) Campbell biology (No. s 1309) Boston: Pearson. 10th edition, Pearson Education, Benjamin Cummings, Australia, 1521.
4. Ree DC, Johnson E, Lewinson O (2009) ABC transporters: the power to change. Nat Rev Mol Cell Biol 10:218-227.
5. Linsdell P (2018) Cystic Fibrosis Trans membrane conductance regulator (CFTR): Making an ion channel out of an active transporter structure. Channels 12:284-290.
6. Liu F, Zhang Z, Csanády L, Gadsby DC, Chen J (2017) Molecular structure of the human CFTR ion channel. Cell 169:85-95.
7. Saint-Criq V, Gray MA (2017) Role of CFTR in epithelial physiology. Cell Mol Life Sci 74:93-115.
8. Hwang TC, Yeh JT, Zhang J, Yu YC, Yeh HI, et al. (2018) Structural mechanisms of CFTR function and dysfunction. J Gen Physiol 150:539-570.
9. Hwang TC, Kirk KL (2013) The CFTR ion channel: gating, regulation, and anion permeation. Cold Spring Harb Perspect Med 3:009498.
10. Zwick, Esposito C, Hellstern M, Seelig A (2016) how Phosphorylation And Atpase Activity Regulate Anion Flux Though The Cystic Fibrosis Transmembrane conductance regulator (CFTR). J Biol Chem 291:14483-14498.
11. Miller C (2010) CFTR: break a pump, make a channel. Proc Natl Acad Sci USA 107:959-960.
12. Hanssens LS, Duchateau J, Casimir GJ (2021) CFTR Protein: Not Just a Chloride Channel? Cells 10:2844.