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Molecular Locksmiths: How Porins Pick and Choose What Enters the Bacterial Cell

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Abstract: The tiny pores present in the external membrane of mitochondria and gram-negative bacteria are made up of proteins known as porins. These are water-filled and control the diffusion of small molecules in and out of cells. Porins are categorized into two main groups: general porins and specific porins. While specific porins are smaller and have a specific selectivity for particular molecules, general porins are non-specific and allow the passage of a large spectrum of tiny molecules. Porins have an influence on antibacterial resistance. The best example of porin-influenced bacterial resistance is the case of Ompf porin in *Escherichia coli.* Porins have the ability to diffuse beta-lactamases from cells. Some of the porins are mutated to smaller sizes. Mutated porins affect the diffusion process of bacteria, by inhibiting these porin the in-and-out movement of waste material from bacteria and the transport of antibiotics can be affected.

Keywords: Porins, Mitochondria, Antibiotics, *Escherichia coli*

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Introduction

Antibiotic resistance is bacteria's ability to inhibit the effects of antibiotics and become resistant to them. Antibiotic resistance is a global problem affecting public health worldwide. The antibiotic resistance in bacteria is occurring due to the misuse, overuse, and unnecessary use of antibiotics. The antibiotic resistant bacteria are leading more due to societal and economic issues. 700,000 cases of antibiotic resistance are globally considered annually, but according to the World Health Organisation, these will increase by more than 10 million by 2050, highlighting a health concern not of secondary importance (Mancuso *et al*., 2021).

Bacteria are constantly evolving and changing their genetic mechanisers to be resistant to

antibiotics. These changes in genetic machineries help them survive and develop in a nasty environment. The most common genetic mechanisms of antibiotic resistance in bacteria are enzymes (ß-lactamases), these enzymes hydrolyse the beta-lactamase or efflux pumps, which expel the antibiotic outside the bacterial cell, the research was conducted by Uddin *et al*. (2021) and Williams *et al*. (2023). Gram-negative bacteria's durability is largely dependent on their cell membranes and their adaptation to various environments. These membranes serve as a barrier for the entry and exit of compounds from the bacterial cell, as well as protecting the bacteria from the eternal environment. The external membrane of bacteria is made of mainy proteins; these porins play a vital role in facilitating the transport of a wide range of molecules, including nutrients, waste products, and antibiotics, across the cell envelope of bacteria (Shea and Moser, 2015; Pages *et al*., 2018).

This inherent resistance mechanism poses a significant challenge in treating gram-negative infections using conventional antimicrobial agents. To effectively combat gram-negative infections, researchers are exploring alternative strategies that target specific components of the envelope of a bacterial cell or disrupt their assembly. One promising approach involves targeting the porins (Heins *et al*., 1994).

Porins and the Classification of Porins

Porins are considered as gatekeepers of bacterial cells. Porins are a diverse group of transmembrane proteins that are formed of water-filled pores in Gram-negative bacteria's outer membranes as well as mitochondria. They aid in the diffusion of small molecules through the external membrane; this process is critical for bacteria's survival. This process allows them to remove waste materials from the cell and allow nutrients to enter (Heins *et al*., 1994; Pages *et al*., 2008). Porins are classified into two classes (general porins and specific porins) based on their substrate specificity (Choi and Lee, 2019).

General porins:

These are non-specific ß-barrel structures with 16 or 18 transmembrane ß- strands, allowing a wide range of molecules to pass through them.

Specific porins:

These are small in size and do not allow the bigger molecules to pass through them. They can be separated into two more groups-- (i) Small solute porins allow small molecules, including carbohydrates, amino acids, and antibiotics, pass through this; and (ii) Large solute porins enable larger molecules like maltose and ß-lactams to enter. Based on their history of evolution, porins can also be categorized. There are five main porin superfamilies (Welte *et al*., 1995; Yen *et al*., 2002).

- *Porin superfamily I* (*PSF I*): These are present in mitochondria and Gram-negative bacteria. It is the largest and most diverse porin superfamily. It contains both general and specific porins.
- *Porin superfamily II* (*PSF II*): These are found in actinomycetal. These are the smaller porin superfamily, a phylum of bacteria that includes many soil-dwelling organisms.
- *Porin superfamily III* (*PSF III*): This is a small porin super family that is found in eukaryotic organelles, such as mitochondria.
- *Porin superfamily IV* (*PSF IV*): This is a small porin super family that is found in eukaryotic organelles, such as the golgi apparatus and the endoplasmic reticulum.
- *Porin superfamily V* (*PSF V*): This is a small porin superfamily that is found in eukaryotic organelles, such as the peroxisome and the glyoxysome.

Role of porins in antibacterial resistance

Bacteria have become resistant to antibiotics in a number of ways that also involve the production of porins. The porins play a very important role in resistance because they help in the exchange of antibiotics from the bacterial cell. Among all the

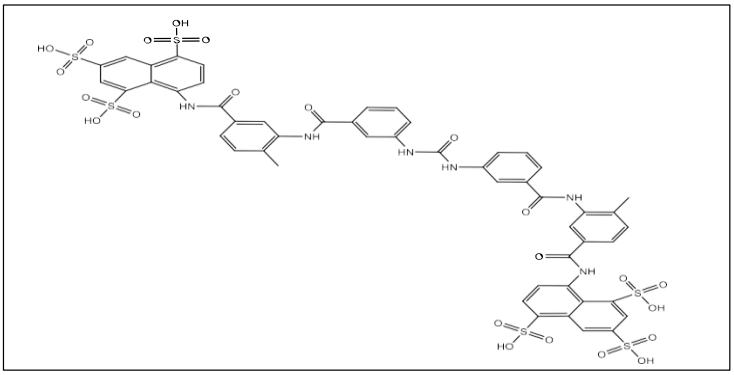

Fig. 1: Suramin.

studied examples of porin- induced resistance to antibiotics is the case of the OmpF porin of *Escherichia coli*, which is normally permeable to beta-lactamase antibiotics such as penicillin and cephalosporins. However, mutant strains of the *E. coli* form of OmpF have a smaller pore size, which does not allow them to be excluded from the cell. Antibiotic resistance mediated by porins is not exclusive to ß-lactam drugs (Kim *et al*., 2020; Saxena *et al*., 2023). Other types of antibiotics, such as fluoroquinolones and macrolides, can also be excluded from cells by porins.

The future of porins

Porins have become an important tool for drug discovery and the development of new drugs for antibiotic-resistant bacteria. Porins are essential for the survival of bacteria and mitochondria, and they are also playing an important role in anti-bacterial resistance by transporting a number of materials in and out of bacterial cells. These are the major targets for antibiotic researchers (Delacour, 1997). Scientists are working to develop compounds that are not affected by porins and are also trying to find out the compounds that inhibit these porins to treat bacterial infections. Porins were also studied for their potential use in treating other diseases like cancer and inflammatory bowel disease. Porins have the capability to transport a variety of molecules, including drugs and therapeutic proteins into cells. This makes them a potentially useful tool for drug delivery (Fernández and Hancock, 2012).

Porin inhibitors

These are the compounds that demonstrate their potential by inhibiting porins and inhibiting antibiotic transport in and out of cells.

Suramin: Suramin, a naphthylsulfonic acid compound, has broad-spectrum antiparasitic properties. From the literature, it has been proven that it inhibits the porin OmpF in *Escherichia coli.* Structurally, suramin exhibits a unique molecular architecture (Fig. 1). Suramin is a complex compound with broad-spectrum biological effects. It interferes with energy production and protein synthesis. Additionally, suramin inhibits the bacterial porin OmpF, a protein essential to facilitate the transportation of small molecules across the external layer of *Escherichia coli* (Barrett, 2001; Payares *et al*., 2004; Delcour *et al*., 2007).

Phenylalanine-arginine: Phenylalanine-arginine (Fig. 2), a ß-naphthylamide (Phe-Arg-ß-NA), is a tripeptide that is a specific inhibitor of E. coli's porin PhoE (Benz *et al*., 1994).

Imidazolium compounds: It has been shown that two quaternary ammonium compounds (Fig. 3) cetylpyridinium chloride (CPC) and dodecyl trimethyl lammonium bromide (DTAB), block a number of porins, including OmpF and PhoE of *E. coli* (Hancock *et al*., 1983).

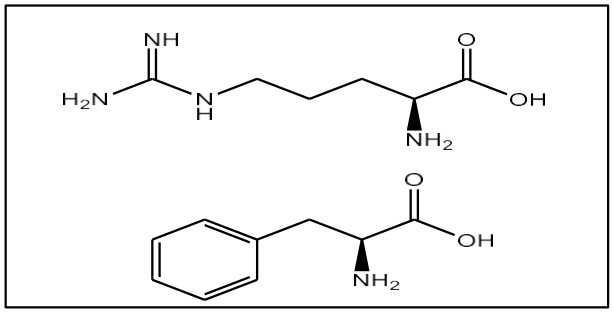

Fig. 2: Phenylalanine-Arginine.

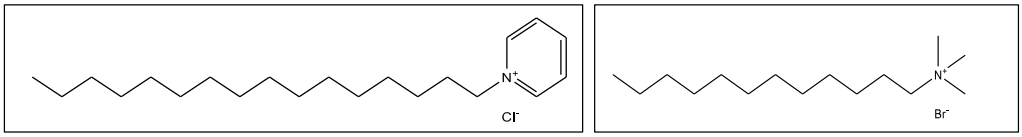

Fig. 3: Cetylpyridinium chloride (CPC) and dodecyltrimethyl ammoniumbromide.

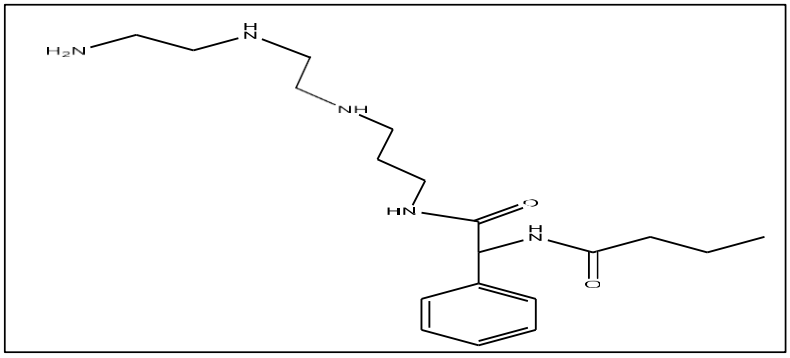

Fig. 4: Philanthotoxin-433(PhTX).

Spermine: A 12-carbon polyamine, Spermine, is a potent inhibitor of OmpF porin in *E. coli.*The polyamine toxins Philanthotoxin-433 (PhTX) (Fig. 4) in the venom of wasps and Joro spider toxin (JSTX) are commonly employed as polyamine-sensitive modulators. These toxins share a distinctive asymmetric structure. One end features a 12-carbon polyamine chain that anchors the molecule within the porin's constriction zone, whereas the other end is characterized by large aromatic groups, creating a molecular dimension comparable to the porin's narrowest point (Basle and Delcour, 2001).

Antimicrobial peptides: Defensins and magainins, naturally occurring antibacterial peptides, have demonstrated the ability to inhibit porins (Brodersen *et al*., 1998).

Conclusion

Porins are essential proteins that are vital for the endurance and proper operation of mitochondria and gram-negative bacteria. They make it easier for tiny molecules to cross the outer membrane, which permits waste elimination and vital nutrition exchange. Porins also play a role in antibiotic resistance. From the literature, it has become clear that a number of porin inhibitors, including suramin, phenylalanine-arginine-ß-naphthylamide, imidazolium compounds, and antimicrobial peptides, are being investigated as potential therapeutic agents to combat antibiotic-resistant bacteria. Further research is needed to fully clarify the mechanisms of porin-mediated

resistance to antibiotics and develop effective porin inhibitors to address this growing public health concern.

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Conflict of Interest

The authors declare no conflicts of interest.

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