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'Traffic' in our cells works both for and against us

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A mechanism that permits essential substances to enter our cells while at the same time removing from them harmful components also has a "down side." This negative aspect prevents vital drugs, such as anti-cancer drugs, from achieving their designed functions, while also enabling bacterial cells to develop resistance to penetration of antibiotics.

A study aimed at a fuller understanding of how this selective mechanism works—with a view towards better controlling it through new drug designs—is the subject of an article by Hebrew University of Jerusalem and German researchers that. has been published in *Proceedings of the National Academy of Sciences* (*PNAS*).

The trafficking of materials in and out of cells is controlled by a variety of proteins found in the membrane surrounding living cells, called "transporters." It is these transporters that fulfill the important function of allowing entrance of vital compounds on the one hand and disposal of toxic compounds on the other hand.

While providing an essential survival strategy for the organism, the transporters that remove toxic compounds from the cell have been associated with the ability of the bacterial cell to develop resistance to antibiotics. In mammalian cells, transporters are responsible for some types of resistance of cancer cells to antineoplastic drugs (drugs against abnormal/cancerous growths). Since this resistance poses serious problems in the treatment of cancers and infectious diseases, these

proteins are an important target for drug design.

To progress in this pursuit, a more complete knowledge of the transporter mechanism is required, but despite many studies, this mechanism is not yet fully understood. It is, however, well established that an essential part of the mechanism stems from the ability of the transporter to change conformations. Thus, the binding site of a particular transporter is alternatively exposed either to the cell cytoplasm (interior) or to the outside environment, enabling the protein to bind its materials on one side of the cell and transport them to the other side.

The research conducted by the Hebrew University-German team focused at a model transporter expressed in the brain: VMAT (Vesicular MonoAmine Transporter). VMAT is known to transport a variety of neurotransmitters like adrenaline, dopamine and serotonin. In addition, it can also transport MPP, a neurotoxin involved in models of Parkinson's disease.

A functional and structural link between VMAT and bacterial transporters responsible for multidrug resistance may suggest a common origin for both types of proteins. A number of studies demonstrated the significance of VMAT as a target for drug therapy in a variety of pathologic states, such as high blood pressure, hyperkinetic movement disorders and Tourette syndrome.

Provided by Hebrew University of Jerusalem

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