Note

THE 1ST CROATIAN SYMPOSIUM ON MEMBRANE TRANSPORTERS (1. HRVATSKI SIMPOZIJ O TRANSPORTERIMA): A SHORT INTRODUCTION TO THE RELEVANCE OF RESEARCH ON TRANSPORTERS

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Organisms are not isolated systems at equilibrium. Cells within an organism must exchange compounds with their environment by passing them across their biological membranes. In eukaryotic cells, transport across membrane-bound organelles such as the nucleus, endoplasmic reticulum, and mitochondria also occurs. Compounds commonly exchanged across membranes include metabolites such as glucose and pyruvate; ions such as sodium, potassium, calcium, and chloride; as well as amino acids and nucleotides. In addition, these cells have to deal with the uptake and/or efflux of numerous endo- and xenobiotics and their metabolites. Essential components in this process are proteins called membrane transporters. Briefly, they effectively carry various molecules to where they are needed, thus enabling the organism to run the metabolism, maintain the intracellular homeostasis of ions and other nutrients, perform functions, resist xenobiotics and pathogens, and make them more tolerant to internal and external stress and adverse conditions. Furthermore, contrary to traditional thought that most lipophilic substances enter cells by passive diffusion, it has recently become evident that very few molecules enter or leave cells, or cross organellar membranes, without the aid of proteins. Even the transport of molecules such as water and urea, which exhibit a limited diffusion across pure phospholipid bilayers, is largely accelerated by transport proteins. The human genome comprises at least 530 genes for plasma membrane transporters (1.7 % of total genes) and 350 genes for intracellular membrane transporters (1.1 % of total genes), which in terms of percentages is not much, but they do code for many proteins that are vital for cell functions.

There are two major classes of membrane transport proteins: carrier proteins and channel proteins (ion channels and aquaporins). Carrier proteins (also called carriers, permeases, or transporters) bind the specific solute to be transported and undergo a series of conformational changes in order to transfer the bound solute across the membrane. Among them is a large superfamily of Solute Carriers (SLC in humans/Slc in animals and prokaryots; secondary or tertiary active transporters that include ion-coupled transporters, exchangers, facilitative transporters, etc.), which in humans contain 52 SLC gene families. Another superfamily of carrier proteins are ABC (ATP Binding Cassette; ABC in humans/Abc in animals and prokaryots) transporters, widely distributed in prokaryots and eukaryots, which bind and use the energy of hydrolysed ATP to transfer molecules across membranes (primary-active transporters). Channel proteins, on the other hand, need not bind the solute. Instead, they form hydrophilic pores that extend across the lipid bilayer. As for ion channels, in most cases their permeability depends on the pore opening; some types of pores are permanently open, whereas the opening-dependent function of others can be regulated

by intracellular or (less common) extracellular effectors. When these pores are open, they allow specific solutes (usually inorganic ions of appropriate size and charge) to pass through them and thereby cross the membrane. Thus far, more than 300 different types of ion channels have been described in living cells. Aquaporins (AQPs) are permanently open transmembrane protein-forming pores specialized for the passive permeability of water and a few other nonpolar molecules such as urea, ammonia, and glycerol. They exist in different forms in animal, plant, and prokaryotic cells. In mammalian cells, 13 different AQPs have been described thus far, whereas in plant and bacterial cells this number exceeds 150.

Therefore, in order to understand the nature of interactions of any single substance with cells and organisms at various levels of biological organization, it is necessary to understand how a particular substance enters the body (or the cell in the first place), how it is distributed from the entry site, how it is metabolized/transformed, and finally, how it is excreted out of the cell and organism, according to today's widely accepted conceptual framework known as ADME (Adsorption, Distribution, Metabolism, Excretion). As membrane transporters are critically involved in all of these processes, and defects in the expression and/or function of transporters lead to the manifestation of numerous clinical disorders, the underlying physiology of the phenomenon has been studied extensively. Likewise, the inhibition of transporters that efflux xenobiotics and their metabolites out from the cells and tissues of various animals has been shown as a harmful event of paramount ecotoxicological relevance, since the inhibition of the transport causes an increase in the accumulation and subsequent toxic effects of numerous xenobiotics that would have otherwise been pumped out of the cells.

Nevertheless, despite its overall importance in the fields of biomedical pharmacology, cancer research and environmental toxicology, the research on membrane transporters in Croatia, as well as in the Western Balkan region in general, has been and is being carried out by only a few research groups. Therefore, as an attempt to get transporter research to a higher level of quality, recognition, and collaboration among research groups in Croatia and abroad, we organized the 1st Croatian Symposium on Membrane Transporters (SOT-1). During the Symposium, the corresponding research by Croatian groups will be presented in an informal, workshop-like atmosphere, the actual level of knowledge in this area summarized, critical research drawbacks highlighted, and potential collaborative initiatives identified and discussed among participants. Abstracts of the presentations held at the Symposium (Zagreb, 6 June – 7 June) are included on the pages that follow.