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Review

Systems biology of ion channels and transporters in tumor angiogenesis: An omics view☆

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ABSTRACT

Solid tumors require the formation of new blood vessels to support their growth, invasiveness and metastatic potential. Tumor neovascularization is achieved by vasculogenesis from endothelial precursors and by sprouting angiogenesis from preexisting vessels. The complex sequence of events driving these processes, including endothelial activation, proliferation, migration and differentiation, is associated with fluxes of ions, water and other small molecules mediated by a great pool of ion channels and transporters (ICT). This 'transportome' is regulated by environmental factors as well as intracellular signaling molecules. In turn, ICT play a prominent role in the response to angiogenesis-related stimuli through canonical and 'unconventional' activities: indeed, there is an increasing recognition of the multifunctionality of several ion channels that could also be annotated as receptors, enzymes, scaffolding proteins, mechanical and chemical sensors.

The investigation of ICT structure and function has been far from the experimental oncology for long time and these two domains converged only very recently. Furthermore, the systems biology viewpoint has not received much attention in the biology of cancer transportome. Modulating angiogenesis by interference with membrane transport has a great potential in cancer treatment and the application of an 'omics' logic will hopefully contribute to the overall advancement in the field.

This review is an attempt to apply the systems biology approach to the analysis of ICT involved in tumor angiogenesis, with a particular focus on endothelial transportome diversity. This article is part of a Special Issue entitled: Membrane channels and transporters in cancers.

Contents

1. Introduction

Over the last thirty years, much insight has been gained into the central role of the endothelium in human health and disease [1]. Endothelial cells (EC) represent a great evolutionary novelty in vertebrates

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[2–5]: they line the blood vessel and act as a dynamic interface between blood and tissues providing a powerful control system for blood pressure and remodeling of vascular network [6]. Since the endothelium can be a target or a causal factor of human disease, its assessment is a valuable tool in clinical investigation [1]. The integrated evaluation of endothelial function and dysfunction incorporating, for example, coagulation, inflammatory, and vascular tone properties in normal homeostasis and diseases led some authors to propose the concept of 'endotheliome' [7]. This term refers to *endotheli*-al form and function as a whole (*-ome*): a key requirement is to forge a synthesis of the array of endothelial vascular modifications in function of time and to understand how they are required for a given function or dysfunction to occur.

The formation of new blood vessels is required during tissue growth and remodeling in order to provide adequate nutrients and oxygen and overcome the basic surface/volume constraint in biological processes. Neovascularization can occur through different mechanisms such as vasculogenesis from endothelial precursors and sprouting angiogenesis [8]. During this process endothelial homeostasis is regulated by pro- and anti-angiogenic factors: the response to these extracellular stimuli depends, among the other proteins, on the plasma-membrane transportome, the great and diversified tool of ion channels and transporters (ICT) expressed in the plasma membrane of EC [9]. Neovascularization actually involves activation, proliferation, migration and differentiation of EC and endothelial cell precursors (EPC): all these events are associated with fluxes of ions, water and other small molecules mediated by a great variety of ICT [10,11]. The growing interest on the contribution of ICT is clearly revealed by the huge number of very recent reports and reviews focused on this topic and published in a broad range of journals [10,12–17].

The transportome is finely regulated by a large pool of intracellular and extracellular signals, respectively, including signaling/metabolic pathways and soluble pro- and anti-angiogenic peptides, hormones, as well as extracellular matrix components. In turn, they mediate the vascular responsiveness to vasoactive stimuli. Intriguingly, this role is not always played by their canonical activity: indeed, as discussed below, a number of ion channels exhibit non-conductive functions and could also be annotated as receptors, enzymes, scaffolding proteins, mechanical and chemical sensors [18–23].

2. ICT expression during normal and altered angiogenesis

Globally, the main aims for a systems biology of ICT in altered angiogenesis should be 1) a clear definition of the endothelial transportome and 2) a deep knowledge of its integration with cell signaling and metabolome (the complete set of small molecule metabolites found within a cell compartment) involved in patho-physiological neovascularization: the latter issue is strictly related to protein interactomics (Fig. 1).

To address the first goal we need an exhaustive annotation of the entire pool of ICT expressed by EC and EPC, their topological distribution and a description of the great variability due to genetic and epigenetic factors, including tissue microenvironment. The readout of this approach would be particularly attractive for vascular biology due to the great diversity found in normal and tumor-associated vessels and endothelial cells [24,25].

Despite the importance and the increased utility of proteomic tools in medical research for extending basic understanding in vascular biology and for directing the delivery of therapeutic and imaging agents in vivo, endothelial proteomics is only at its beginning. In addition, global ontology analyses are required to move beyond a simple list of proteins and to understand better how they interact and function in a given environment, providing a validation of a proteome generated from large-scale mass spectrometry (MS) analysis. This would lead to a better knowledge of the relationship of proteins in a functional network, as well as to the detection of novel functions and pathways in the given tissue [26].

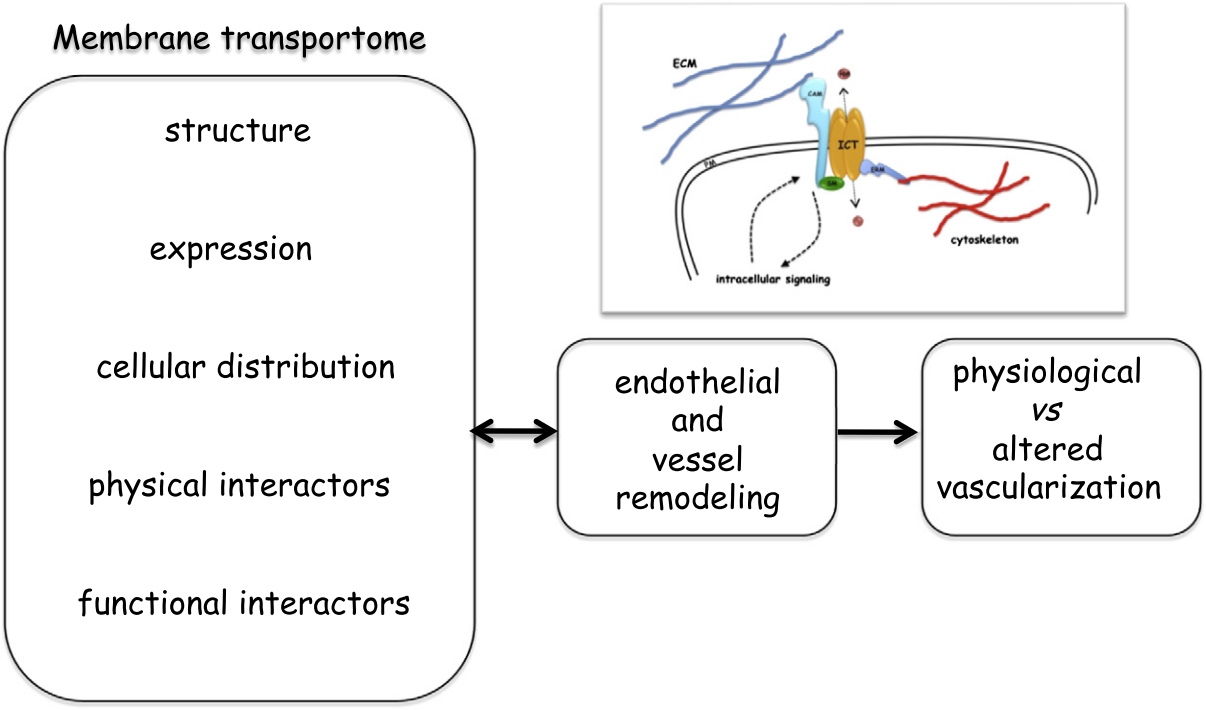

Fig. 1. Conceptual scheme for an integrated view of membrane transportome and its role in tumor vascularization. The inset picture shows the ICT embodied in multiprotein complexes involving extracellular matrix (ECM), cytoskeleton and true intracellular signaling network. ERM: ezrin, radixin, and moesin family of proteins. CAM: cell adhesion molecules. SM: scaffolding and signaling molecules.