Molecular Aspects of Medicine 34 (2013) 719–734

Contents lists available at SciVerse ScienceDirect

Molecular Aspects of Medicine

journal homepage: www.elsevier.com/locate/mam

Review

Solute carriers (SLCs) in cancer ☆

Sara El-Gebali [a,b,1], Susanne Bentz [a,b,1], Matthias A. Hediger [a,b], Pascale Anderle [a,b,c,d,*]

[a] Institute of Biochemistry and Molecular Medicine, University of Bern, Bern, Switzerland
[b] Swiss National Centre of Competence in Research, NCCR TransCure, University of Bern, Switzerland
[c] Swiss National Centre of Competence in Research, Molecular Oncology, Swiss Institute for Experimental Cancer Research, Ecole Polytechnique Fédérale de Lausanne, School of Life Sciences, Lausanne, Switzerland
[d] Swiss Institute of Bioinformatics, Lausanne, Switzerland

Guest Editor Matthias A. Hediger
Transporters in health and disease (SLC series)

ARTICLE INFO

Article history:
Received 1 October 2012
Accepted 13 December 2012

Keywords:
Solute carrier
SLC
Cancer
Chemo-sensitivity
EMT
Stem cells
Drug target

ABSTRACT

During tumor progression cells acquire an altered metabolism, either as a cause or as a consequence of an increased need of energy and nutrients. All four major classes of macromolecules are affected: carbohydrates, proteins, lipids and nucleic acids. As a result of the changed needs, solute carriers (SLCs) which are the major transporters of these molecules are differently expressed. This renders them important targets in the treatment of cancer. Blocking or activating SLCs is one possible therapeutic strategy. For example, some SLCs are upregulated in tumor cells due to the increased demand for energy and nutritional needs. Thus, blocking them and turning off the delivery of fuel or nutrients could be one way to interfere with tumor progression. Specific drug delivery to cancer cells via transporters is another approach. Some SLCs are also interesting as chemosensitizing targets because blocking or activating them may result in an altered response to chemotherapy. In this review we summarize the roles of SLCs in cancer therapy and specifically their potential as direct or indirect targets, as drug carriers or as chemosensitizing targets.

Contents

☆ Publication in part sponsored by the Swiss National Science Foundation through the National Center of Competence in Research (NCCR) TransCure, University of Bern, Switzerland; Director Matthias A. Hediger; Web: http://www.transcure.ch.

* Corresponding author at: Institute of Biochemistry and Molecular Medicine, University of Bern, Buehlstrasse 28, CH-3012 Bern, Switzerland. Tel.: +41 0 31 631 4739; fax: +41 0 31 631 3410.
E-mail address: pascale.anderle@ibmm.unibe.ch (P. Anderle).

[1] These authors contributed equally to this work.

0098-2997/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.mam.2012.12.007

1. Hallmarks of cancer and SLCs

Cancer is a gradually developing disease that follows several well-defined steps. It arises due to the accumulation of genetic mutations or epigenetic alterations that drive the process of malignancy. Tumor progression was described by Hanahan and Weinberg as a process in which a number of genetic changes are essential to confer growth advantages necessary for the conversion of normal cells to cancer cells (Hanahan and Weinberg, 2000). They described six main alterations that ultimately lead to the malignant transformation (Fig. 1):

- Sustaining proliferative signaling: self-sufficiency in growth signals.
- Evading growth suppressors: insensitivity to anti-growth signals.
- Resisting cell death/apoptosis: evading apoptosis.
- Sustained angiogenesis.
- Activating invasion: metastasis.
- Enabling replicative immortality: limitless replication.

However due to the rapid progress in the field of cancer research two hallmarks of cancer have emerged: avoiding immune destruction and deregulating cellular energetics (Hanahan and Weinberg, 2011).

Membrane transporters are the gatekeepers for cells and organelles thereby controlling uptake and efflux of vital compounds. Membrane transporters include members of the Solute Carrier (SLC) series as well as ABC transporters, ion and water channels, aquaporins, and pumps. The BioParadigms website provides a list of transporter families of the SLC series (see http://www.bioparadigms.ch). Currently, it includes 52 families encompassing ion coupled transporters, exchangers and passive transporters expressed at the plasma membrane or in intracellular organelles (e.g. mitochondrial or vesicular transporters). The SLC series includes transporters of a diverse range of substrates such as sugars, amino acids, vitamins, nucleotides, inorganic ions, trace minerals and drugs.

Membrane transporters can be exploited in various ways in cancer therapy (Fig. 2). Inhibiting or activating transporter function is one possible therapeutic strategy. For example, some SLCs are upregulated in tumor cells due to the increased demand for energy and nutritional needs. Modulating their activity can have a direct influence on biological processes relevant for tumor growth and invasion. Some SLCs may serve as chemo-sensitizing targets resulting in an altered response to chemotherapy. Specific drug delivery to cancer cells via active transport is another approach. Influx carriers that are overexpressed in tumor cells may increase chemo-sensitivity, whereas secretion pumps/efflux carriers may be inhibited to reduce chemo-resistance.

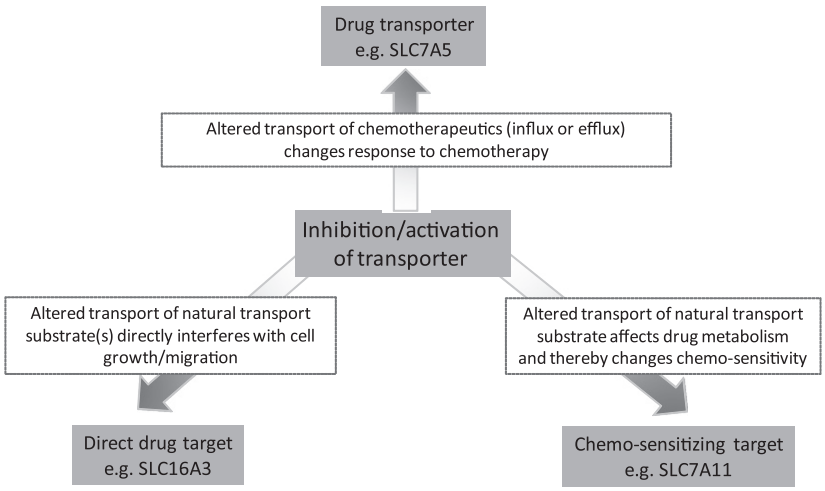

Fig. 1. Role of transporters in cancer therapy.