A Putative Role of Organic Anion Transporting Polypeptides (Oatps) In Cell Survival of Hormone-Dependent Breast and Prostate Cancers

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Abstract

Transporter proteins classified into the solute carrier (SLC) transporter superfamily are essential for import of nutrients for cell survival in organisms. In the last two decades, compelling evidence has accumulated that SLC transporters interact with clinically important anticancer agents and contribute to their pharmacokinetics, particularly the biopharmaceutical processes of absorption, elimination and distribution. Furthermore, many SLC transporters have been shown to be differentially upregulated in cancer cells, and this may represent an adaptive response to altered nutritional requirements. Thus, it is likely to utilize them as carrier for efficient drug delivery as well as pharmacological target to shut off the essential nutrients for cell growth of malignant tumors. This short review will introduce organic anion transporting polypeptides which recognize endo- and exogenous organic anionic compounds and recent findings about their upregulation in cancer cells. Besides, OATP-mediated sulfate conjugates of steroid hormone may contribute to cell survival and adapted growth under hormone-depleted conditions. Better understandings of pathophysiological role of OATPs likely provide key information to overcome hormone-refractory breast and prostate tumors.

Abbreviations

ADT: Androgen Deprivation Therapy; CRPC: Castration Resistant Prostate Cancer; E3S: Estrone-3-Sulfate; DHEAS: Dehydroepiandrosterone Sulfate; FDG: 2-[fluorine-18]-Fluoro-2-Deoxy-D-Glucose; OATP: Organic Anion Transporting Polypeptide; PET: Positron Emission Tomography; mTOR: Mammalian Target of Rapamycin; SLC: Solute Carrier; STS: Steroid Sulfatase.

Keywords

SLC transporters; OATP; Hormone-refractory cancer; Chemotherapy; Breast; Prostate

Introduction

Membrane transporter proteins encoded by a number of gene families may play important role in cell survival because they are essential for import of key nutrients, which is hydrophilic and impermeable to plasma membranes by itself, including glucose and amino acids. It is collectively known that many influx transporters classified into solute carrier transporter (SLC) superfamily are upregulated in malignant tumors, although their physiological relevance has to be determined.

For instances, enhanced expression of glucose transporter GLUT1/SLC2A1 in cancer cells is a molecular target for cell entry of the most common PET imaging agent in clinical use, FDG (2-[fluorine-18]-I fluoro-2-deoxy-D-glucose), allowing to diagnose where malignant tumors are located [1,2]. Besides, several transporter proteins for amino acids such as leucine and glutamine have been well documented to be upregulated in many types of cancer cells, [3,4] showing their critical role in nutrient signaling to mTOR and cell growth [5]. In addition to amino acid transporter, we have shown that enhanced activity of peptide transport in cancer cells [6,7]. Thus, differential upregulation of influx transporter could be utilized not only to efficiently deliver...
their substrate drug with anti-tumor activity [3,7] or diagnost-
ic markers [4,8,9], but also to shut off nutrient essential for
cell growth; therefore, they can be promising target for a new
chemotherapy. In this short review, we introduce our recent
progresses regarding pathophysiological role of enhanced or-
ganic anion transporting polypeptides, OATPs, in cell prolif-
eration of hormone-dependent breast and prostate cancers,
implying pharmacological intervention of OATPs may con-
tribute to efficient eradication of cancer cells.

OATPs

Organic Anion-Transporting Polypeptides (OATPs) are cur-
rently classified into the SLCO family consisting of 12 indi-
vidual members, which have been basically characterized
capable of transporting wide range of organic anionic com-
ounds [10,11]. Human cDNAs of OATP1A2, 2B1, 1B1, 3A1
and 4A1 were originally identified in our laboratory [12] and
roles of OATP2B1, 1B1 and 1A2 among those in drug pharma-
cokinetcis and disposition have been well established by many
researchers [11,12]. Members of this family generally medi-
ate Na+-independent transport of amphipathic organic anion
compounds and their substrates include bile salts, steroid
conjugates, thyroid hormones and oligopeptides [11] as well
as numerous drugs including major anticancer agents such as
methotrexate[13], paclitaxel [14], SN-38 [15], and decetaxel
[16]. Recent progresses about OATP family members in drug
metabolism and disposition were reviewed in [17,18] with
sumarized list of their substrates. Nowadays, it becomes
convincing that expression of OATP molecules are enhanced
in many types of cancer cells; however, there is no established
rationale why they are over-expressed and how they contribu-
t to cell growth in malignant tumors.

Enhanced Expression in OATPs in Cancer Cells

OATP1B3 is one of the most studied OATPs in cancer cells, and
has been documented its enhanced expression in gastric, colo-
rectal, and pancreatic breast cancer, but not hepatocellular
carcinomas [13,19]. Lee et al [20] detected OATP1B3 protein
expression in 75 out of 93 patient-derived colon adenocar-
cinomas (81%) and no immunostaining in normal samples,
and more interestingly OATP1B3 exhibited antiapoptotic ef-
fect, providing a survival advantage by altering p53-dependent
pathways [20], although substances transported by OATP1B3
was not identified in relation to the effect in the research.
They later found that colon cancer cells express truncated form of
OATP1B3 with limited transport activity because of missing
the first 28 amino acids [21]. Independently, similar observation
was made in cancer-type isoform of OATP1B3 mRNA
that is expressed in colon and lung cancer cells. Since it was
described to lack 47 amino acids at N-terminus, it may not be
identical to the former one [22]. Thus, differences in expres-
sion and function may provide a clue to understand to clinici-
significance of OATP1B3 expression in cancer. Collectively
OATP1B3 recognizes and transports major anticancer agents;
therefore, such differential expression of OATP1B3 may de-
terminate their efficacy in chemotherapy, thereby resulting in
providing a clinical benefit.

In addition to OATP1B3, other OATPs are also known to be
highly expressed in cancer cells. A recent study with patient-
derived prostate tumor specimens indicates that mRNA ex-
pression of six SLCO genes, including SLCO1B3 and 2B1, was
enhanced several-fold in castration resistant prostate cancer
metastases, compared to untreated prostate cancer, implying
their association with prostate cancer-specific motility [23].
Previous research suggests OATP1B3 is involved in transport
of testosterone [24]. Overall survival of patients with prostate
cancer in response to ADT therapy is affected by genetic vari-
ants of SLCO2B1 and SLCO1B3. Therefore, OATP may help
prostate cancer cells to increase gonadal androgen availability
[25]. Many groups including us have also implied possibil-
ity of overexpression of OATP2A1, OATP3A1, OATP4A1,
OATP5A1, and OATP4C1 in breast cancer cell lines, includ-
ing MCF-7 and T-47D cells [26-28]. OATP1A2 was shown to
be upregulated in neoplastic breast tissues obtained from pa-
tients [29]. Furthermore, remarkable expression of OATP1A2
and 2B1 was reported in patient-derived human gliomas [30].
Considering the wide spectrum of substrate specificity of these
transporters, these observations suggest that the transporters
are one of determinants of efficacy of their substrate anti-cancer
agents.

Role of OATPs in Hormone Dependent Cancer Cells

Breast cancer: It is known that steroid sulfatase (STS) activity is
often detected in breast cancer cells at a considerably higher
level than aromatase. STS catalyzes a hydrolysis of sulfate
dependent substrates. This hypothesis is tested by feeding horm-
ones to breast cancer cells. Although it remains necessary
for breast tumor progression in cooperation with STS. This hypothesis is tested by feeding hormone-responsive breast cancer cells with E3S to observe their growth, and then eventually used to generate biologically active
estrogen by breast cancer cells, more likely, under estradiol-
depleted conditions such as post-menopausal women. Since
OATPs efficiently facilitate cell entry of hydrophilic E3S, they
may contribute to breast tumor progression in cooperation
with STS. This hypothesis is tested by feeding hormone-respon-
sive breast cancer cells with E3S to observe their growth. A significant increase in MCF-7 [26] and
T-47D [27] cell growth was observed. Furthermore, we have
recently shown that OATP1B3 is differentially upregulated in
a sub-population of MCF-7 cells, suggesting that OATP1B3
serves as E3S transporter to allow breast cancer to survive
under depletion of active estrogen such as estradiol [31].
This notion is also supported by enhanced STS expression corre-
lated with increased expression of breast cancer tumors in 120 clinical
specimens [32]. Increased expression of OATP1A2, which can
transport E3S, mediated by PXR in breast tumor tissues fed
with E3S supports this as well [17,9]. These observations sug-
genot OATPs at least in part contributes to tumor growth
by regulating hormone dependency providing an adopted cell
survival of breast cancer cells. Although it remains necessary
to clarify the contributions of these OATPs to tumor growth, it is
conceivable that developing a potent OATP inhibitor with
high affinity kills efficiently hormone refractory breast cancer
that acquired by in treatment with aromatase inhibitors such as
anastrozole and letrozole.
Prostate cancer: In human prostate cancer, gonadal androgens is critical for protein synthesis and cell survival [33]. Endocrine therapy that removes gonadal testosterone or antagonizes androgen receptors is currently a mainstream to treat prostate cancer. Although this Androgen Deprivation Therapy (ADT) is efficient, the disease may progress to the stage of Castration-Resistant Prostate Cancer (CRPC). Once CRPC is developed, it no longer responds to ADT. Since CRPC tumor progression is still considered to be associated with enhanced androgen receptor (AR) function [34-36], residual androgen availability, e.g. adrenocortical androgen, may be involved in the progression. In addition to E3S, OATPs can translocate dehydroepiandrosterone sulfate (DHEAS), [11,37,38] which is a thousand fold more abundant than testosterone in human serum [39] and is basically unchanged by ADT. DHEAS is hydrolyzed to DHEA by STS [40] and then can further be converted to androstenedione, a weak androgen in prostate cancer [41], thereby resulting in stimulation of AR function (Figure 1), [42]. We have studied role of OATPs in an experimental CRPC cell culture model and recently reported OATP-mediated DHEAS is important for cell survival of prostate cancer [43]. Cell growth of AR-positive LNCaP cells was stimulated with DHEAS (Figure 2A) and the stimulation was abolished by an STS inhibitor, STX64. mRNA expression of various OATP genes were up regulated in LNCaP and 22Rv1 cells under androgen-depleted conditions [43]. Because OATP1A2 mRNA expression increased most prominently among those genes in LNCaP cells grown in androgen-depleted medium, LNCaP cells with OATP1A2 gene being silenced were established and designated KD16 and KD34. In both KD16 and 34 cells, the DHEAS-induced cell growth was not observed, compared to the control C3 and C9 cells (Figure 2B), [43]. Our results suggest that enhanced OATP1A2 expression is associated with adaptive cell growth of prostate cancer cells under androgen-depleted conditions. Thus, OATPs including OATP1A2 may play an essential role in rescuing prostate cancer cells from shortage of androgen such as testosterone by feeding DHEAS and utilizing it as a source of androgen in interplay of STS. This provides a new rationale to complement current endocrine therapy in combination use of an efficient inhibitor for OATPs if developed.

Figure 1: Hypothesized role of OATPs in cell survival in prostate cancer cells under gonadal androgen depletion condition

Testosterone plays a role in cell growth and proliferation of prostate cancer cells and crosses the plasma membranes by simple diffusion by itself. Testosterone is converted to dihydrotestosterone (DHT) by 5α-reductase (5αR), and then binds to androgen receptor (AR). DHT-bound AR homodimerizes, enters nuclear and regulates gene expression so that it proceeds cell growth and releases PSA. Under the condition where testosterone is deprived of, cell entry of abundant plasma DHEAS may be facilitated by enhanced OATPs and DHEAS can be converted to DHEA, a weak androgen, by steroid sulfatase (STS), whose expression is not affected by availability of androgens. Since DHEA is converted to testosterone by multiple enzymatic reactions, handling DHEAS can be converted to DHEA, a weak androgen, by steroid sulfatase (STS), whose expression is not affected by availability of androgens. Since DHEA is converted to testosterone by multiple enzymatic reactions, handling DHEAS by interplay of OATPs and STS may impart vulnerable prostate cancer cells an alternative source of androgens.


