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Review

Arylsulfatases A and B: From normal tissues to malignant tumors

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ABSTRACT

Arylsulfatases are lysosomal enzymes with important roles in the cell metabolism. Several subtypes of arylsulfatase are known, from A to K. Congenital deficiencies of arylsulfatases, especially A (ARSA) and B (ARSB), can induce metabolic disorders such as metachromatic leucodystrophy (ARSA deficiency) and Maroteaux-Lamy syndrome (ARSB deficiency). ARSA and ARSB pseudodeficiencies were recently described but their exact roles are far to be known. The aim of this review was to synthesize the literature data, combined with personal results, regarding the roles of ARSA and ARSB in non-tumor disorders but also carcinogenesis. Few than 50 published papers regard ARSA and ARSB expression in cancer. They suggest decreased activity of these arylsulfatases in most of carcinomas, compared with normal tissues. However, the clinical impact is still unknown. Further complex studies are necessary to be done, to understand the role of ARSA and ARSB expression in cancer.

1. Introduction

Sulphatases are lysosomal enzymes, playing roles in several physiological processes, but their specific functions in tumors are far to be known [1]. As arylsulfatases can be expressed in tissues such liver, skin, lymph nodes, nervous tissue [2], we aimed to perform a literature review regarding the basic roles of arylsulfatases A and B (ARSA and ARSB) in tumors. As non-tumor pathology is necessary to highlighted too, the paper was structured in three main parts: general data, roles of ARSA and ARSB in non-tumor disorders, respectively ARSA and ARSB functions in tumors.

2. Methodology

This review was synthesized based on the papers included in the PubMed/Medline database, which were published between 1967 and 2018 and regards expression of ARSA and ARSB. For performing a database search, the following keywords were used: ARSA, ARSB, ARSA and cancer, ARSB and cancer, ARSA and carcinoma, ARSB and carcinoma, ARSA and melanoma, ARSB and melanoma.

Experimental, original and descriptive researches were considered, excluding duplicate records, letters, meta-analysis and papers without significant information. Articles about other arylsulfatases, except ARSA and ARSB, were also excluded.

Based on the criteria mentioned above, from more than 7000 articles, only 1813 were firstly selected. Then, a number of 152 articles were taken into account, with furter selection of 57 papers, for detailed analysis (Fig. 1).

3. General data about ARSA and ARSB

3.1. ARSA

ARSA gene is a 14-kb gene with eight exons, each of them having 103–320 nucleotides [3]. It encodes ARSA protein, a lysosomal enzyme known to catalyze degradation of sulfatides into galactosylceramides (GalC), starting with the hydrolysis of a sulfate residue [4,5]. The resulting molecules are reused, as precursors for sulfatide biosynthesis. This recycling pathway breaks down when ARSA does not hydrolyze properly, and the resupply for biosynthesis is missing [6]. Beside accelerated degradation through ARSA hydrolysis, abnormal translocation, defects in biosynthesis and other mechanisms can induce sulfatide deficiency [7].

ARSA deficiency is caused by chromosomal mutations in the *ARSA* gene. The direct effect of its deficiency occurs only if the other parts of the metabolic cycle are intact [8,9].

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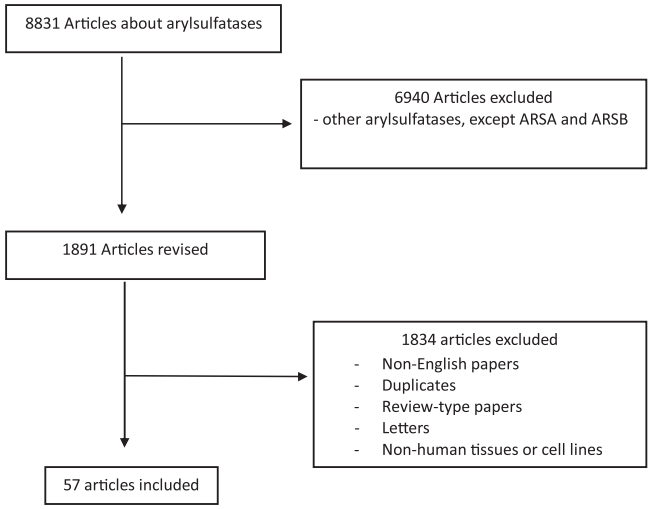

Fig. 1. PRISMA diagram adapted for data about arylsulfatases A and B (ARSA and ARSB) in the PubMed database, between 1968 and 2018.

More than 150 pathologic allelic variations of ARSA, associated with ARSA deficiency, have been reported [8,10]. It is about micro-deletions, insertions or point mutations [11].

The most common gene alterations are c.465 + 1G > A, c.542 T > G and c.1283C > T. These disorders were found in half of the Caucasian population. Other relatively rare polymorphism and neutral base changes (c.98 T > C, c.195Cdel, c.229 G > C, c.545C > G, c.674A > G, c.852 T > A, c.1274A > G) have also been reported, but their exact role is still unknown [8–11].

Splice site mutations and insertions or deletions lead to abnormal gene product, with no active enzyme. Between 20% and 50% of the single aminoacid changes are associated with low level (< 1%) of ARSA enzyme activity, altered enzyme or intensified turnover of the mutant protein [12,13].

3.2. ARSB

ARSB is mainly localized in lysosomes. Tissues such as hepatic, renal, pancreatic and human colonic epithelium, can express ARSB [14–16]. The main role of ARSB it to break-down glycosaminoglycan (GAG) into dermatan- and chondroitin sulfate [17].

The role of ARSB is described within the Kegg's pathway: key-enzyme of the degradation of sulfatides is localized in lysosomes, removing 4-sulfate groups from the non-reducing end of chondroitin 4-sulfate and dermatan sulfate, and inducing further degradation. ARSB deficiency is caused by mutations in the *ARSB* gene and can be treated with enzyme replacement therapy [18,19].

3.3. ARSA and ARSB interaction

ARSA and ARSB are mainly lysosomal enzymes. However, they can appear in sinusoidal endothelial cells, being co-expressed with heparan sulfate, to create extracellular matrix [20]. Besides lysosomes, ARSA and ARSB can also be expressed by endothelial cells. A relation between chondroitin 4-sulfation, ARSB activity, and cellular phenotype was suggested [21–26].

4. ARSA and ARSB roles in non-tumor disorders

4.1. ARSA total deficiency and metachromatic leukodystrophy

ARSA knock-out mice and patients with total ARSA deficiency present metachromatic leukodystrophy [8,9,27]. This lysosomal storage disorder was firstly described in the early '80 s and is characterized by the accumulation of cerebroside sulfate within lysosomes [27,28]. It further induces myelin accumulation of sulfatides and destruction of white matter [27]. Metachromatic leukodystrophy is characterized by progressive deterioration of intellectual function and motor skills. Evolution depends on the period of occurrence of symptoms [3,27–29]. In early childhood, it leads to rapid deterioration and is frequently lethal. Its occurrence in childhood (over 4 years old) and adolescence period associates a survival rate that crosses 20 years after diagnosis. Diagnosis in adult life induces a survival rate over 20–30 years after diagnosis [3,27–29].

4.2. ARSB total deficiency and Maroteaux-Lamy syndrome

Overall deficiency of ARSB leads to Maroteaux-Lamy syndrome, which is a rare autosomal recessive type VI mucopolysaccharidosis [18,19]. The organism can not break down glycosaminoglycans, which are stored as large sugar chains within bones, cartilages, cornea, skin, and connective tissue. The organs can be enlarged, inflamed or scarred but, unlike other types of mucopolysaccharidoses, brain function is not deteriorated. Conformation of the head, face, internal organs, and respiratory system can be modifed. Muscular-skeletal system can also be affected [30].

4.3. ARSA and ARSB roles in uro-genital system

Both ARSA and ARSB play roles in proper function of female and male reproductive system. In premenopausal women, ARSA is upregulated during the ovulatory phase and shows low activity during the early follicular phase. ARSB has low activity in the follicular phase and is upregulated during the luteal phase. High ARSA levels can be a predisposing factor of developing endometrial polyps [31–33].

The normal function of spermatozoa and seminal fluid is also supposed to be related by arylsulfatases. Low ARSA/ARSB levels in seminal fluid can induce male sterility [34,35].

In patients with protein-overload nephropathy, gene expression of hepatic cerebroside sulfotransferase is down-regulated (Table 1), which induces a reduction of liver and serum sulfatides [26]. Although the relationship between kidney function and level of sulfatides is proved, the molecular mechanism of this interaction is still unknown [36,37].

4.4. ARSB and other non-tumor disorders

Cystic fibrosis is known to be induced by mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which causes disorders of epithelial cells secretion. Recent data shows that ARSB can also be involved in the pathophysiology of this condition, by impaired metabolism of GAGs (glycosaminoglycans) [38].

It was also suggested that ARSB upregulation may play a role in carotid atherosclerosis associated with cerebral embolization but also in other processes such disorders of extracellular matrix [39] (Table 1).

5. ARSA and ARSB roles in tumors

In the early 90 s, researchers start investigation of ARSA expression in cancers of gastrointestinal tract, breast, lung, central nervous system, kidney, and female genital tract. Their findings suggest that both ARSA and ARSB may play roles in tumorigenesis and metastatic potential of tumor cells [40]. Few than 50 studies were published in this field, most of them being based on cell lines (Table 2).

5.1. Malignant melanoma

In the only one paper related to ARSB expression in melanoma [41], it was showed that low activity of ARSB in melanoma cell lines associates increased invasiveness. It happens via overexpression of CSPG4 (chondroitin sulfate proteoglycan) and MMP2 (matrix

Table 1
Key-studies regarding arylsulfatases (ARS) roles in non-tumor disorders.

Reference	Year of publication	Enzyme	Experiment type	Results
Gieselmann et al	1989	ARSA	N-glycosilation site study	Underglycosilated ARSA is less stable with lower catalytic activity
Echeverri et al	2017	ARSA	In silico predicition	ARSA deficiency affects glycosphingolipid pathways
Kreysing et al	1990	ARSA	ARSA gene study	MLD is caused by microdeletions, insertions or point mutations
Mahshadi et al	2017	ARSA	ARSA gene study	New gene mutations
Bhattacharyya et al	2007	ARSA/ARSB	ARSA/ARSB interaction with estrogen hormones	Marked variation in activity of enzymes
Vitaioli et al	1985	ARSA/ARSB	ARSA/ARSB activity in endometrium	Fluctuation of enzyme activity during ovulatory phase
Keiko et al	2009	ARSA/ARSB	ARSA/ARSB activity in liver	Lysosomal and nonlysosomal localization of enzymes in the liver
Sardiello M et al	2005	ARSA/ARSB	Arylsulfatase gene localization	Gene mapping for arylsulfatases
Seljelid R et al	1968	ARSA/ARSB	Localization study	Activity in cytosomes in thyroid follicules
Daniele et al	1998	ARSA/ARSB	Functional analysis	Mutations linked to congenital disorders
Hanson SR et al	2004	ARSA/ARSB	Enzyme study	Comprehensive overview how sulfatases can hydrolyse sulfate esters
Frese MA et al	2007	ARSA/ARSB	Functional study	Competitive inhibition by phosphates
Zhang et al	2009	ARSA/ARSB	Gene expression study	Protein overload nephropaty down-regulates gene expression
Kwiatkowska et al	2017	ARSA	ARSA acivity study	Predicition of early and late graft function
Bhattacharyya et al	2007	ARSB	ARSB activity in cystic fibrosis	Increased activity with successful correction of the genetic defect in cystic fibrosis
Bhattacharyya et al	2015	ARSB	Modified activity of ARSB in cystic fibrosis	CFTR modifiers can reduce accumulation of ARSB end products
Biros E et al	2017	ARSB	Gene expression study	Upregulation of ARSB in atherosclerosis associated with embolizaton effects

metalloproteinase), which are known as melanoma progression factors [41–45]. ARSB can provide MMP activation and remodelling of the extracellular matrix by removing 4-sulfate groups from the non-reducing end of chondroitin-4-sulfate [42–45]. No papers about ARSA expression in melanoma cells were published yet.

5.2. Colorectal cancer

Few than 20 Medline papers regard ARSB expression in colorectal cancer (CRC) cells. In 2009, Bhattacharyya et al. demonstrated ARSA and ARSB positivity in the human colonic epithelium [16] but no specific data about ARSA expression in CRCs were published yet. Their study shown that ARSB play a key role in CRC cells invasivness and metastasis [16], the fact being confirmed by authors [21–26]. ARSB can also influence the migratory capacity of colonic epithelial cells, from normal (NCM460) to malignant cell lines (T84) [21–26].

As the activity of ARSB is reduced in CRC cells, compared to the normal colonic tissue, it was suggested that ARSB cytoplasmic positivity can be an indicator of malignancy [16,46].

ARSB silencing can affect other genes expression, especially of MMP9 and Ras homolog gene family (RhoA) [21–26,47–51]. It can also act through Wnt signaling pathway [47]. ARSB might influence one of the three major types of Wnt signaling pathway: canonical, non-canonical cell polarity and non-canonical Wnt-calcium pathway [47–49]. Other pathomechanism of decreased expression of ARSB in CRC cells, compared to normal colonic epithelium, is related to increased expression of Chondroitin-4-sulfate, with binding Sp1 to Wnt9A promoter, and further upregulation of the Wnt9A expression [41–45,47–49].

A poorly understood phenomenon is the so called Warburg-effect, a condition related to malignant transformation of normal colonic epithelium [50]. As the ARSB function needs a proper oxygen level, downregulation might be related on carcinoma-related hypoxia, an well known phenomenon of malignancy [50].

Other phenomenon of CRC aggressivity is the epithelial-mesenchymal transition (EMT). It refers to transformation of tumor epithelial cells in mesenchymal-like cells [52]. This phenomenon can be induced by several factors, including platelet-derived growth factor (PDGF), which produces dissolution of adherens junctions [53]. Dysfunctional PDGFRa can result from ARSA deficiency, highlighting the potential role in of ARSA in CRC behavior [54,55] (Table 2).

5.3. Lung cancer

In the two papers published in Medline database, regarding lung cancer and arylsulfatases, it was proved increasing ARSA and ARSB enzyme activity in lung carcinomas, compared to normal parenchyma [55,56].

5.4. Urogenital cancer

Few than 10 Medline-indexed articles refer to arysulfatases roles in urogenital carcinomas. Feferman et al suggested that ARSB could be used as a biomarker of prostate cancer [57]. ARSB intensity is down-regulated in prostate carcinoma cells, compared with normal tissue, and shows inverse correlation with Gleason score [57]. No other studies regarding these correlations were published yet.

Table 2
Key-studies regarding arylsulfatases (ARS) roles in tumors.

Reference	Year of publication	Enzyme	Experiment type	Results
Bhattacharyya S et al	2017	ARSB	Gene expression study	Low ARSB activity leads to high invasiveness in melanoma
Bhattacharyya S et al	2009	ARSB	Gene expression study	ARSB expression effects on colonic epithelial cell migration capacity
Pituch KC et al	2015	ARSA	Protein expression study	ARSA deficiency can reduce platelete derived growth factors
Fuchs W et al	1985	ARSB	Metabolic study	Alternative pathways in formation of ARSB
Gasa S et al	1983	ARSB	Protein expression study	Possible role of ARSB in human lung cancer
Feferman L et al	2013	ARSB	Immunoassay study	ARSB as prognostic biomarker in prostate cancer, inverse correlation between ARSB immunostaining (rabbit polyclonal antibody) and Gleason score
Laidler P et al	1991	ARSA	Radioimmunoassay study	High ARSA activity can be predictive in malignancy
Gasa S et al	1980	ARSA/ARSB	Enzyme activity with anion-exchange chromatography	Possible role of the two arylsulfatases in human lung cancer

In bladder cancer, ARSA activity is upregulated [58] but the clinical impact is still unknown.

Using p-nitrocatechol sulfate-based biochemical methods, it was proved decreased level of ARSA in endometrial polyps, compared with normal endometrium [31–33].

In breast carcinoma cell lines, both ARSA and ARSB proved to have lower activity, compared to normal cells [30], without confirmation in clinical studies.

6. Personal experience

In 2015 a comparative study has been done by our team about arylsulfatase A in different chronic pathologies, as end stage renal disease, Parkinson's disease, type 2 diabetes, prostate cancer and HIV infection, demonstrating significant changes in chronic kidney disease, type 2 diabetes and Parkinson syndrome [58]. The study was based on spectrophotometric serum determination of arylsulfatase A activity. There is no relevant data in the literature about ARSA and ARSB influence on oncological treatment efficiency at this point.

7. Future perspectives

Despite the several studies published about pathomechanisms of ARSA and ARSB in non-tumor diorders, the exact mechanism still remains unknown. Moreover, their role in carcinogenesis is far to be elucidated. Further complex studies are necessary to be performed, for understanding the relation between ARSA/ARSB and molecular pathways of cancer that includes MMP-related cell matrix remodelling, Wnt pathway or angiogenesis.

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References

[1] S. Lamouille, J. Xu, R. Derynck, Molecular mechanisms of epithelial-mesenchymal transition, Nat. Rev. Mol. Cell Biol. 15 (2014) 178–196.
[2] K.W. Selcer, H.M. DiFrancesca, A.B. Chandra, L. Pui-Kai, Immunohistochemical analysis of steroid sulfatase in human tissues, J. Steroid Biochem. Mol. Biol. 105 (2007) 115–123.
[3] J. Kreysing, K. von Figura, V. Gieselmann, Structure of the arylsulfatase A gene, Eur. J. Biochem. 191 (1990) 627–631.
[4] S.R. Hanson, M.D. Best, C.H. Wong, Sulfatases: structure, mechanism, biological activity, inhibition and synthetic utility, Angew. Chem. Int. Ed. Engl. 43 (2004) 5736–5763.
[5] H. Ramakrishnan, K.K. Hedayati, R. Lullmann-Rauch, C. Wessig, S.N. Fewou, H. Maier, H.H. Goebel, V. Gieselmann, M. Eckhardt, Increasing sulfatide synthesis in myielin forming cells of arylsulfatase-A deficient mice causes demyelination and neurological symptoms reminiscent of human metachromatic leukodystrophy, J. Neurosci. 27 (2007) 9482–9490.
[6] P. Fredman, J.E. Mansson, B.M. Rynmark, K. Josefsen, A. Ekblond, L. Halldner, T. Osterbye, T. Horn, K. Buschard, The glycosphingolipid sulfatide in the islets of Langerhans in rat pancreas is processed through recycling: possible involvement in insulin trafficking, Glycobiology 10 (2000) 39–50.
[7] X. Han, D. Holtzman, D.W. McKeel Jr, J. Kelley, J.C. Morris, Substantial sulfatide deficiency and ceramide elevation in very early Alzheimer's disease: potential role in disease pathogenesis, J. Neurochem. 82 (2002) 809–818.
[8] M. Blomqvist, V. Gieselmann, J.E. Mansson, Accumulation of lysosulfatide in the brain of arylsulfatase A deficient mice, Lipids Health Dis. 10 (28) (2011).
[9] J. Bohringer, R. Santer, N. Schumacher, F. Gieseke, K. Cornils, M. Pechan, B. Kustermann-Kuhn, R. Handgretinger, L. Schols, K. Harzer, I. Krageloh-Mann, I. Muller, Enzymatic characterization of novel arylsulfatase A variants using human arylsulfatase A-deficient immortalized mesenchymal stromal cells, Hum. Mutat. 38 (2017) 1511–1520.
[10] T. Schuster, A. Muhlstein, C. Yaghootfam, O. Maksimenko, E. Shipulo, S. Gelperina, J. Kreuter, V. Gieselmann, U. Matzner, Potential of surfactant-coated nanoparticles to imrpove brain delivery of arylsulfatase A, J. Control. Release 253 (2017) 1–10.
[11] M.D. Manshadi, B. Kamalidehghan, O. Aryani, E. Khalili, S. Dadgar, M. Tondar, F. Ahmadipour, G.Y. Meng, M. Houshmand, Four novel ARSA gene mutations with pathogenic impacts on metachromatic leukodystrophy: a bioinformatics approach to predict pathogenic mutations, Ther. Clin. Risk Manag. 13 (2017) 725–731.
[12] N. Gomez-Ospina, et al., Arylsulfatase A deficiency, May 30 [Updated 2017 Dec 14], in: M.P. Adam, H.H. Ardinger, R.A. Pagon (Eds.), GeneReviews, University of Washington, Seattle, Seattle (WA), 2006, pp. 1993–2019.
[13] R. von Bulow, B. Schmidt, T. Dierks, N. Schwabauer, K. Schilling, E. Weber, I. Uson, K. von Figura, Defective oligomerization of arylsulfatase A as a cause of its instability in lysosomes and metachromatic leucodistrophy, J. Biol. Chem. 277 (2002) 9455–9461.
[14] S. Hanson, M.D. Best, H.C. Wong, Sulfatases: structure, mechanism, biological activity, inhibition, and synthetic utility, Angew. Chemie Int. Ed. 43 (2004) 5736–5763.
[15] S. Bhattacharyya, L. Feferman, J. Tobacman, Defining the role of arylsulfatase B (N-acetylgalactosamine 4-sulfatase) in cellular metabolism, FASEB J. 29 (2015) 16.
[16] S. Bhattacharyya, J. Tobachman, Arylsulfatase B regulates colonic epithelial cell migration by effects on MMP9 expression and RhoA activation, Clin. Exp. Metastasis 26 (2009) 535–545.
[17] P. Harmatz, R. Shediac, Mucoplysaccharidosis VI: pathophysiology, diagnosis and treatment, Front. Biosci. 22 (2017) 385–406.
[18] C. Ittiwut, S. Boonbuamas, C. Srichomthong, R. Ittiwut, K. Suphapeetiporn, V. Shotelersuk, Novel mutations, including a large deletion in the ARSB gene, causing mucopolysaccharidosis type VI, Genet. Test. Mol. Biomarkers 21 (2017) 58–62.
[19] P. Harmatz, C.J. Hendriksz, C. Lampe, J.J. McGill, R. Parini, E. Leao-Teles, V. Valayannopoulos, T.J. Cole, R. Matousek, S. Graham, N. Guffon, A. Quartel, The effect of galsulfase enzyme replacement therapy on the growth of patients with mucoplysaccharidosis VI (Maroteaux-Lamy syndrome), Mol. Genet. Metab. 122 (2017) 107–112.
[20] M.N. Keiko, K. Shinichiro, K. Hayato, A. Koji, A. Yoshihiro, Cell-surface arylsulfatasae A and B on sinusoidal endothelial cells, hepatocytes and Kuppfer cells in mammalian livers, Med. Mol. Morphol. 42 (2009) 63–69.
[21] M. Sardiello, I. Annunziata, G. Roma, A. Ballabio, Sulfatases and sulfatase modifying factors: and exclusive and promiscuous relationship, Hum. Mol. Genet. 14 (2005) 3203–3217.
[22] R. Seljelid, H.J. Helminen, The localization of arylsulfatase activity in thyroid cells, J. Histochem. Cytochem. 16 (1968) 467–472.
[23] A. Daniele, G. Parenti, M. d'Addio, G. Andria, A. Ballabio, G. Meroni, Biochemical caracterization of arylsulfatasae E and functional analysis of mutations found in patients with X-linked chondrdysplasia punctata, Am. J. Hum. Genet. 62 (1998) 562–572.
[24] S.R. Hanson, M.D. Best, C.H. Wong, Sulfatases: structure, mechanism, biological activity, inhibition, and synthetic utility, Angew. Chem. Int. Ed. Engl. 43 (2004) 5736–5763.
[25] M.A. Frese, S. Schulz, T. Dierks, G. Arylsulfatase, A novel lysosomal sulfatase, J. Biol. Chem. 283 (2008) 11388–11395.
[26] X. Zhang, T. Nakajima, Y. Kamijo, G. Li, R. Hu, R. Kannagi, M. Kyogashima, T. Aoyama, A. Hara, Acute kidney injury induced by protein-overload nephropathy down-regulates gene expression of hepatic cerebroside sulfotransferase in mice, resulting in reduction of liver and serum sulfatides, Biochem. Biophys. Res. Commun. 390 (2009) 1382–1388.
[27] M.D. Crawford, The metabolic basis of inherited disease, J. Clin. Pathol. 36 (8) (1983) 961.
[28] V. Gieselmann, A. Polten, J. Kreysing, K. von Figura, Arylsulfatase A pseudodeficiency: loss of a polyadenylation aignal and N-glycosilation site, Proc. Natl. Acad. Sci. U.S.A. 86 (1989) 9436–9440.
[29] P.O.Y. Echeverri, A.D. Salazar, A. Rodriguez-Lopez, J. Gonzalez, C.J. Almeciga-Diaz, A.L. Barrera, Understanding the metabolic consequences of human arylsulfatase A deficiency through a computational systems biology study, Cent. Nerv. Syst. Agents Med. Chem. 17 (2017) 72–76.
[30] S. Bhattacharyya, J. Tobacman, Steroid sulfatase, arylsulfatase A and B, Galactose-6-sulfatase, and iduronate sulfatase in mammary cells and effects of sulfated and non-sulfated estrogens on sulfatase activity, J. Steroid Biochem. Mol. Biol. 103 (2007) 20–34.
[31] L. Vitaioli, G. Gobbetti, E. Baldoni, Arylsulfatase A activity and sulphatide concentration in the female rabbit oviduct are under physiological hormonal influence, Histochem. J. 28 (1996) 149–156.
[32] L. Vitaioli, E. Baldoni, E. Fioretti, Fluctuation in arylsulfatase activity in the rabbit endometrium during the sexual cycle, Histochemistry 83 (1985) 127–131.
[33] P. Oner, S. Bekpinar, F. Cinar, A. Argun, Realtionship of some endogenous sex steroid hormone to leucocyte arylsulfatase A activities in pre and postmenopausal healthy women, Hormone Metabol. Res. 26 (1994) 301–304.
[34] S.P. Dandekar, P. Harikumar, Seminal profiles of lysosomal enzymes in normal and infertile men, J. Postgrad. Med. 43 (1997) 33–37.
[35] B.M. Gadella, B. Colenbrander, L.M. van Golde, M. Lopes-Cardozo, Boar seminal vesicles secrete arylsulfatases into seminal plasma, Biol. Reprod. 48 (1993) 483–489.
[36] E. Kwiatkowska, L. Domanski, J. Bober, K. Safranow, A. Pawlik, K. Ciechanowski, Activity of urine arylsulfatase A in brain-dead graft donors is a predictor of early and late graft function, Postepy Hig. Med. Dosw. 71 (2017) 1–4.
[37] S. Bhattacharyya, D. Look, J.K. Tobacman, Increased arylsulfatase B activity in cystic fibrosis cells following correction of CFTR, Clin. Chim. Acta 380 (2007) 122–127.
[38] S. Bhattacharyya, L. Feferman, J.K. Tobacman, Effect of CFTR modifiers on arylsulfatase B activity in cystic fibrosis and normal human bronchial epithelial cells, Pulm. Pharmacol. Ther. 36 (2016) 22–30.
[39] E. Biros, C.S. Moran, J. Maguire, E. Holliday, C. Levi, J. Golledge, Upregulation of arylsulfatase B in carotid atherosclerosis is associated with symptoms of cerebral embolization, Sci. Rep. 7 (2017) 1–7.

[40] P. Laidler, D. Kowalski, J. Silberring, Arylsulfatase A in serum from patients with cancer of various organs, Clin. Chim. Acta 203 (1991) 69–77.
[41] S. Bhattacharyya, L. Feferman, K. Terai, A.Z. Dudek, J.K. Tobacman, Decline in arylsulfatase B leads to increased invasiveness of melanoma cells, Oncotarget 8 (2017) 4169–4180.
[42] J.F. deSousa Jr, H.B. Nader, C.P. Dietrich, Sequential degradation of chondroitin sulfate in molluscs, J. Biol. Chem. 265 (1990) 20150–20155.
[43] J.H. Glaser, H.E. Conrad, Chondroitin SO4 catabolism in chick embryo chondrocytes, J. Biol. Chem. 254 (1979) 2316–2325.
[44] B. Ingmar, A. Wasteson, Sequential degradation of a chondroitin sulfate disaccharide by lysosomal enzymes from embryonic-chick epiphyseal cartilage, Biochem. J. 179 (1979) 7–13.
[45] S. Bhattacharyya, J.K. Tobacman, Arylsulfatase B regulates colonic epithelial cell migration by effects on MMP9 expression and RhoA activation, Clin. Exp. Metastasis 26 (2009) 535–545.
[46] S.V. Prabhu, S. Bhattacharyya, G. Guzman-Hartman, V. Macias, A. Kajdacsy-Balla, J. Tobackman, Extra-lysosomal localization of arylsulfatase B in human colonic epithelium, J. Histochem. Cytochem. 59 (2011) 328–335.
[47] S. Bhattacharyya, L. Feferman, J. Tobacman, Increased expression of colonic Wnt9A through Sp1-mediated transcriptional effects involving arylsulfatase B, chondroitin 4-sulfate and galectin-3, J. Biol. Chem. 289 (2014) 17564–17575.
[48] H. Clevers, Wnt/B-catenin signaling in developement and disease, Cell 127 (2006) 469–480.
[49] T. Reya, H. Clevers, Wnt signaling in stem cells and cancer, Nature 434 (2005) 843–850.
[50] S. Bhattacharyya, L. Feferman, J. Tobacman, Restriction of aerobic metabolism by aquired or innate arylsulfatase B deficiency: a new approach to the Warburg effect, Sci. Rep. 6 (32885) (2016).
[51] E.D. Hay, An overview of epithelio-mesenchymal transformation, Acta Anat. 154 (1995) 8–20.
[52] L. Yang, C. Lin, Z.R. Liu, p68 RNA helicase mediates PDGF-induced epithelial mesenchymal transition by displacing Axin from beta-catenin, Cell 127 (2006) 139–155.
[53] K.C. Pituch, A.L. Moyano, A. Lopez-Rosas, F.M. Marottoli, G. Li, C. Hu, R. van Breemen, J.E. Mansson, M.I. Givogri, Dysfunction of the PDGFRa represses the production of oligodendrocytes from arylsulfatase A deficient multipotential neural precursor cells, J. Biol. Chem. 290 (2015) 7040–7053.
[54] W. Fuchs, M. Beck, H. Kresse, Intralysosomal formation and metabolic fate of N-acetylglucosamine 6-sulfate from keratan sulfate, Eur. J. Biochem. 151 (1985) 551–556.
[55] S. Gasa, A. Makita, Phosphorylation on protein and carbohydrate moieties of a lysosomal arylsulfatase B variant in human lung cancer transplanted into athymic mice, J. Biol. Chem. 258 (1982) 5034–5039.
[56] S. Gasa, A. Makita, T. Kameya, T. Kodama, E. Araki, T. Yoneyama, M. Hirama, M. Hashimoto, Elevated activities and properties of arylsulfatase A and B-variant in human lung tumors, Cancer Res. 40 (1980) 3804–3809.
[57] L. Feferman, S. Bhattacharyya, R. Deaton, P. Gann, G. Guzman, A. Kajdacsy-Balla, J.K. Tobacman, Arylsulfatase B (N-acetylgalactosamine-4-sulfatase): potential role as a biomarker in prostate cancer, Prostate Cancer Prostatic Dis. 16 (2013) 277–284.
[58] Z. Kovacs, R. Tripon, E. Nemes Nagy, V. Balogh Samarghitan, M. Tilinca, O. Martha, Z. Fazakas, Arylsulfatase A: an important metabolic factor in pathophysiology of different diseases, AMM 61 (3) (2015) 233–235.