doi: 10.4149/gpb_2017031

Review

Role of *S*-adenosylmethionine cycle in carcinogenesis

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Abstract. Alterations in enzymatic activities underlying the cellular capacity to maintain functional *S*-adenosylmethionine (SAM) cycle are associated with modified levels of its constituents. Since SAM is the most prominent donor of methyl group for sustaining the methylation pattern of macromolecules by methyltransferases, its availability is an essential prerequisite for sustaining the methylation pattern of nucleic acids and proteins. In addition, increased intracellular concentrations of *S*-adenosylhomocysteine and homocysteine, another two constituents of SAM cycle, exerts an inhibitory effect on the enzymatic activity of methyltranferases. While methylation pattern of DNA and histones is considered as an important regulatory hallmark in epigenetically regulated gene expression, amended methylation of several cellular proteins, including transcription factors, affects their activity and stability. Indeed, varied DNA methylome is a common consequence of disturbed SAM cycle and is linked with molecular changes underlying the transformation of the cells that may underlay the carcinogenesis. Here we summarize the recent evidences about the impact of disturbed SAM cycle on carcinogenesis.

Key words: *S*-adenosylmethionine — DNA methylation — Cancer — Epigenetic regulation— Metabolism

Introduction

The gain or subsequent loss of methyl group by macromolecules plays a significant regulatory role in cellular signal transduction with profound impact on modulation of physiological responses (Jaenisch and Bird 2003; Biggar and Li 2015) on all levels in organism. The methylation status of DNA and histones are considered important epigenetic hallmarks with profound impact on several processes including cellular differentiation, chromosomal organization and stability as well as epigenetically regulated gene expression (Jaenisch and Bird 2003). In addition to histones, also the methylation of several other proteins controls their enzymatic activity, feasibility for protein-protein interaction and stability (Biggar and Li 2015). Dysregulations in processes fundamental for generation, maintaining or removal of methyl moieties from macromolecules has been implicated in etiology of several diseases (Feinberg 2007), including cancer (Jones and Baylin 2002, 2007).

In human cells, along with *S*-adenosylmethionine (SAM) also structural analogues of tetrahydrofolate (THF) serve the roles of methyl-group donors. While, SAM is the most common donor of a methyl group for the substrate-specific methyltransferases, which facilitate the processes of DNA, RNA and protein methylation (Chiang et al. 1996), the structural analogues of THF are mostly involved in synthetic reactions of nucleotides and amino acids. Since, 5-methyl THF is a compound essential for re-synthesis of methionine from homocysteine by methionine synthase (Selhub 2002), it links metabolism of THF with SAM. The metabolism of SAM includes reactions of its synthesis and regeneration, which are arranged in a pathway known as SAM-cycle (Fig. 1). Sustaining of SAM-cycle is dependent on intermediary metabolism and can be negatively affected by a dietary supply of several essential nutrients, e.g., methionine, folate, cobalamin and pyridoxine. Impaired dietary supply, absorption, distribution, metabolism or enzymatic processing of

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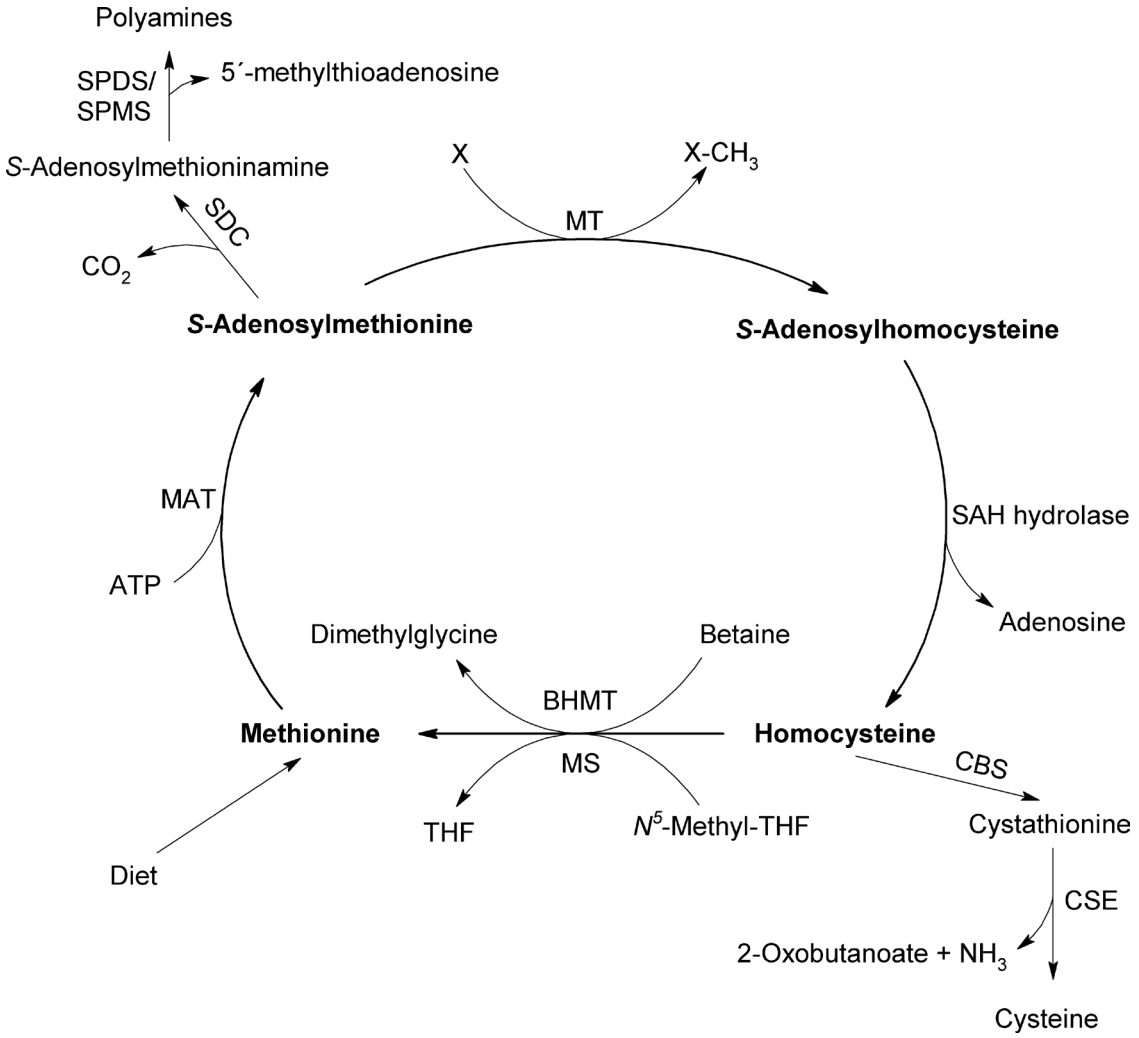

Figure 1. The scheme of the *S*-adenosylmethionine (SAM) cycle. Methionine adenosyltransferase (MAT) converts methionine and ATP to SAM, which subsequently may enter two distinct metabolic pathways. After decarboxylation of SAM to *S*-adenosylmethioninamine by SAM decarboxylase (SDC), it serves a role of aminopropyl group donor for polyamine synthesis enzymatically catalyzed by spermidine synthase (SPDS) and spermine synthase (SPMS). In trans-methylation reactions, catalyzed by methyltransferases (MT), SAM donates methyl group to variety of the substrates and is converted to *S*-adenosylhomocysteine (SAH) that is cleaved by SAH hydrolase to homocysteine and adenosine. Homocysteine is either remethylated to methionine or by transsulfuration reactions converted to 2-oxobutanoate and cysteine. The remethylation may be catalyzed by either of two enzymes, methionine synthase (MS) or betaine homocysteine methyltransferase (BHMT) those require as a source of methyl group either 5-methyl tetrahydrofolate (N^5-Methyl-THF) or betaine, respectively. The transsulfuration pathway requires serine as second co-substrate for cystathionine β-synthase (CBS) to generate cystathionine that is subsequently hydrolyzed by cystathionine γ-lyase (CSE).

these nutrients negatively impacts the cellular level of SAM. Suppressed production of SAM is linked with amendments in methylation reactions of macromolecules. The changes in methylation pattern of macromolecules could increase the risk of cellular transformation leading to cancer (Jones and Baylin 2002, 2007).

Indeed, the results of several performed studies show that deficiency of folate, B_{12}, or methionine are affecting serum and cellular levels of SAM, *S*-adenosylhomocysteine and homocysteine, and are linked with molecular processes contributing to oncogenesis (Lu and Mato 2012; Hirschey et al. 2015). Among others tissues, the liver is the most common and the best studied organ undergoing a cellular transformation to hepatocellular carcinoma due to disturbed capability to maintain physiological SAM level (Ramani et al. 2011; Lu and Mato 2012). Besides the nutritional composition of the diet and a capability of the organism to absorb, metabolize and distribute these essential components to particular tis-

sues, the controlling mechanisms of enzymatic activity of the enzymes participating on the SAM metabolism should be taken into account.

S-Adenosylmethionine metabolism

The enzymatic reactions of formation, transmethylation and further regeneration of SAM are ordered in a cyclic metabolic pathway named SAM-cycle (Fig. 1), which is ubiquitously present across all tissues. The first reaction, the synthesis of SAM from methionine and ATP is catalyzed by methionine adenosyltransferase (MAT; EC 2.5.1.6), also known as SAM synthetase. In cellular metabolism, SAM possesses three distinct functions. SAM can be decarboxylated by SAM decarboxylase [EC 4.1.1.50] to *S*-adenosylmethioninamine, which is a donor of propylamine residue in polyamine synthetic pathway (Fig. 1). The second, the least studied role of SAM in human cells is to donate 5′-deoxyadenosyl radical (Duschene and Broderick 2010). The most prominent metabolic function of SAM is its role of a methyl-group donor in variety reactions catalyzed by enzymes from a methyltransferase family (Fontecave et al. 2004). Indeed, more than 90% of formed SAM molecules are consumed for sustaining the methylation reactions and only up to 5% for the generation of *S*-adenosylmethioninamine. In humans, the liver is the organ with highest turnover of SAM and metabolism of methionine (Mato et al. 2002).

Methyltransferases generate *S*-adenosylhomocysteine, which is subsequently hydrolyzed to homocysteine and adenosine by *S*-adenosylhomocysteine hydrolase [EC 3.3.1.1]. This reversible reaction of *S*-adenosylhomocysteine hydrolysis is characterized by an equilibrium constant lower than one and therefore the reversible synthesis of *S*-adenosylhomocysteine is energetically favorable (Finkelstein 1990). The produced homocysteine is precursor for resynthesis of methionine or donate a sulfhydryl group to serine during cysteine anabolism in an order of two enzymatic reactions catalyzed by cystathionine β-synthase [4.2.1.22] and cystathionine γ-lyase [4.4.1.1]. The both enzymes, cystathionine β-synthase and cystathionine γ-lyase, are vitamin B_6-dependent and among the products of their mutual activity belong cysteine, ammonia, 2-oxobutanoate (Fig. 1) and hydrogen sulfide (Yang et al. 2008; Szabo et al. 2013). Enzymatic conversion of homocysteine to cysteine significantly contributes to maintaining the cysteine level and subsequently also to synthesis of glutathione (Mosharov et al. 2000). Hydrogen sulfide is a gaseous signaling molecule with impact on several cellular (Li et al. 2011), physiological (Yang et al. 2008) and pathophysiological functions (Szabo et al. 2013; Sen et al. 2015). In colon cancer cells, hydrogen sulfide supports cellular bioenergetics, tumor growth and proliferation, as well as promotes angiogenesis and vasorelaxation (Szabo et al. 2013), while hydrogen sulfide released from human breast cancer cells prevents the suppressive effect of activation macrophage on their growth (Sen et al. 2015).

The regeneration of methionine from homocysteine can be catalyzed by two distinct enzymes, either by cobalamin-dependent methionine synthase (Banerjee and Matthews 1990; [EC 2.1.1.13]) or Zn^{2+}-dependent enzyme from thiolmethyltransferase family – betaine homocysteine methyltransferase (Pajares and Pérez-Sala 2006; [EC 2.1.1.5]), which utilize as a co-substrate either 5-methyl THF or betaine, respectively.

In contrast to SAM and *S*-adenosylhomocysteine, the remaining two members of SAM cycle – homocysteine (Tsitsiou et al. 2009) and methionine (Bröer 2008) – can be transported through the plasma membrane by specific transporters. Therefore, increased serum concentration of homocysteine might in addition to inherited genetic diseases also reflect either increased rate of SAM utilization followed by an insufficient regeneration of methionine from homocysteine, or suppressed conversion of homocysteine to cysteine.

Effect of altered expression of *MAT* genes on carcinogenesis

The early observations, that the inhibition of SAM production induced either by ethionine administration (Farber 1963) or methyl-deficient diet (Mikol et al. 1983; Ghoshal and Farber 1984) were followed by hepatocellular carcinoma, the studies focusing on the role of SAM metabolism in carcinogenesis have been initiated. Up today obtained results show that alterations in expression and activity of the enzymes involved in metabolism of SAM (Tab. 1) as well as the conditions associated with the deficiency or availability of essential nutrients, e.g., methionine, folic acid and cobalamin with negative impact on the cellular SAM levels are significant players in etiology in several cancer types (Tab. 1). Among them, the hepatocellular carcinoma is the most prominent cancer type (Lu and Mato 2012; Ramani et al. 2011), which has been most intensively studied.

The synthesis of SAM from methionine by MAT catalyzes reaction that is a rate limiting step in SAM cycle. In human tissues, three isoforms of MAT have been identified, which differ in their structure, tissue location, substrate specificity and kinetic parameters. The both isozymes, MAT I and III, are composed from catalytically active α1 subunits, which are assembled either in homotetrameric or homodimeric form, respectively. The switch between dimeric and tetrameric structures of MAT I/III isozymes impacts the total cellular activity of MAT (Cabrero et al. 1988; Markham and Pajares 2009) and is controlled by methionine availability (Sanchez del Pino et al. 2000). The α1 subunit is a product of *MAT1A* gene with predominant expression in adult liver. The isozyme MAT II consists from two distinct subunits, α2 and β, those

may assembly together into the heterotetrameric structure. Two genes, *MAT2A* and *MAT2B*, are coding protein products α2 and β, respectively; those are widely expressed through the body. While α2 subunit possesses the catalytic activity, the β subunit exerts a regulatory effect on a catalytic activity of α2 subunit. The β subunit lowers the both values of α2 subunit, K_M for methionine and K_i for SAM. Since SAM is a feedback inhibitor of only MAT II isoform, the expression and subsequent co-assembly of the α2 with β subunit suppresses the synthesis of SAM and lower its cellular concentration (Martínez-Chantar et al. 2003a, 2003b).

In contrast to the expression of *MAT1A* gene, which predominates in adult liver, a gene product of *MAT2A* is predominantly expressed in all mammalian tissues and in fetal hepatocytes. Several studies show that the expression of all three genes, *MAT1A*, *MAT2A* and *MAT2B*, is changed in cells of multiple cancer types (Tab. 1). While the expression of *MAT1A* (Cai et al. 1996) is downregulated the levels of both, *MAT2A* (Cai et al. 1996; Liu et al. 2011; Tomasi et al. 2015; Yang et al. 2015) and *MAT2B* (Martínez-Chantar et al. 2003a), gene products are increased. This relates with isozyme switch of MAT I/III to MAT II that leads to lowering

Table 1. Alterations in expression of SAM cycle genes associated with carcinogenesis

Gene	Change	Effect	Cancer type	References
MAT1A	↓ mRNA	↓ Expression of MAT	Hepatocellular carcinoma	Cai et al. 1996
	Coding region methylation	↓ Expression of MAT	Hepatocellular carcinoma	Tomasi et al. 2012
	↓ Expression	↓ Expression of MAT	Cholangiocarcinoma	Yang et al. 2016
MAT2A	↑ Enzyme sumoylation	↑ Bcl-2 expression Suppress apoptosis	Colon cancer cells Liver cancer cells	Tomasi et al. 2015
	↓ Enzyme acetylation	↑ Tumor cell growth	Hepatocellular carcinoma	Yang et al. 2015
	↓ Expression	↑ Tumor cell growth	Renal	Wang et al. 2014
	↑ Expression	↑ Tumor cell growth	Hepatoma cells	Liu et al. 2011
	↑ Expression	↑ Tumor cell growth	Gastric	Zhang et al. 2013
	↑ mRNA	↑ Tumor cell growth	Colon	Chen et al. 2007
	↑ Expression	↑ Tumor cell growth	Leukemic T cells	Halim et al. 2001
MAT2B	↑ Expression	↓ SAM	Hepatocellular carcinoma	Martínez-Chantar et al. 2003a
	Interaction with GIT1	Activation of ERK and MEK	Hepatocellular carcinoma Colon cancer	Peng et al. 2013
		Predicted modified methylation status of DNA	Multiple types	Mehrmohamadi et al. 2016
SAH hydrolase	Mutations	↓ Activity	Kidney Small intestine Pancreas Skin	Leal et al. 2008
	Mutations	↓ Activity	Liver	Stender et al. 2015
BHMT	Mutation	↓ Activity	Hepatocellular carcinoma	Pellanda et al. 2012 Pellanda 2013
	↓ Expression	↑ Tumor size ↑ α-fetoprotein ↑ Vascular invasion	Hepatocellular carcinoma	Jin et al. 2016
BHMT2		Predicted modified methylation status of DNA	Multiple types	Mehrmohamadi et al. 2016
MTR	A2756G polymorphismus	↑ Risk	Retinoblastoma	Akbari et al. 2015
	A2756G polymorphismus	↑ Risk	Lung	Shi et al. 2005
	A2756G polymorphismus	↑ Risk	Colorectal	de Vogel et al. 2009
	A2756G polymorphismus	↑ Risk	Gastric	Kim et al. 2016
MTRR	A66G polymorphism	↑ Risk	Multiple forms	Wang et al. 2017
	A66G polymorphism	↑ Risk	Lung	Shi et al. 2005
	A66G polymorphism	↑ Risk	Colorectal	de Vogel et al. 2009

MAT, methionine adenosyltransferase; *SAH*, *S*-adenosylhomocysteine; *BHMT*, betaine homocysteine methyltransferase; *MTR*, methionine synthase; *MTRR,* methionine synthase reductase; MEK1, mitogen-activated protein kinase kinase; GIT1, G protein-coupled receptor kinase interacting ArfGAP 1; ERK, extracellular signal-regulated kinase.

of SAM concentration (LeGros et al. 2001; Frau et al. 2013) with subsequent dysregulation in methylation of DNA (Frau et al. 2012; Tomasi et al. 2012) and histones with impact on the gene expression (Mentch et al. 2015). The results of the several studies about the effect of the increased *MAT2A* expression revealed that increased level of MAT II isozyme positively enhances the proliferation of cancer stem cells (Lu and Mato 2012) and may potentiate a cancer development and progression (Halim et al. 2001; Chen et al. 2007). In addition, suppressed expression of *MAT2A* gene yielding to the absence of MAT II isoform induces cell cycle arrest and apoptosis as well as suppresses a cancer cell proliferation (Wang et al. 2008; Liu et al. 2011; Zhang et al. 2013). The transcriptional switch from *MAT1A* to *MAT2A* is believed to be a consequence of SAM level decrease with further capability to suppress the negatively influence the level of SAM (Lu and Mato 2012) and facilitates the cancer cell survival and proliferation.

The expression of *MAT2A* gene and its enzymatic activity are regulated at both transcriptional and post-transcriptional levels. The level of *MAT2A* mRNA in hepatocellular cancer cells could be enhanced by several *trans*-activating transcription factors such as: Sp1, c-Myb, NF-κB, AP-1 (Yang et al. 2001, 2003) and HIF-1α (Liu et al. 2011). Moreover, the covalent modifications yielding to histone acetylation, promoter region methylation contribute in regulation of *MAT2A* gene transcription (Frau et al. 2012). On posttranscriptional level, the stability of *MAT2A* mRNA is regulated by RNA-binding protein HuR. HuR can exist in methylated or un-methylated form. While, the presence of methylated HuR protein is associated with destabilization of *MAT2A* mRNA and decreased expression of α2 subunit of MAT II isoform, the un-methylated HuR exerts an opposite effect (Vázquez-Chantada et al. 2010).

Covalent, post-transcriptional modifications of proteins have been identified as an evolutionarily conserved way affecting their enzymatic activities (Zhao et al. 2010). Dysregulations in placing, maintaining or removal of covalent marks on proteins affect their stability and/or activity with profound impact on cellular metabolism and may lead to carcinogenesis (Lin et al. 2013). Since, α2 subunit of MAT II in addition to its enzymatic role in process of SAM synthesis possesses also several signaling functions. Increased acetylation (Yang et al. 2015) or suppressed sumoylation (Tomasi et al. 2015) of α2 subunit exerts anti-proliferative effect on cancer cells. While an acetylation of α2 subunit promotes its ubiquitination and subsequent proteasomal degradation and represses the tumor growth (Yang et al. 2015), sumoylation of α2 subunit is linked with its increased stability and enhanced expression of Bcl-2 protein leading to cancer cell survival and growth (Tomasi et al. 2015). The regulatory role of MAT α2 subunit on the expression could be mediated by its interaction with several transcription factors and capability to function as a transcriptional co-repressor (Katoh et al. 2011; Kera et al. 2013; Tomasi et al. 2015). In colon and hepatic cancer cells, also the expression of β subunit of MAT II positively correlates with their survival, due to a capability of β subunit to assembly with GIT1 protein (G protein coupled receptor kinase interacting ArfGAP 1) to a complex that activates ERK and MEK signaling pathways those are subsequently promoting the cancer cell growth (Peng et al. 2013).

In addition to above mentioned molecular mechanisms affecting the cellular level of SAM mediated by altering the expression of MAT isoforms, the enzymatic activity of MAT I/III may be further regulated by free radicals (for review see: Corrales et al. 2002). The primary structure of MAT α1 protein contains conserve cysteine 121 residue of which reduces sulfhydryl group is essential for sustaining the enzymatic activity. Conversion of this free sulfhydryl group by any reaction with the thiol-reacting compounds or insufficient capacity to regenerate it by reduced glutathione inhibits the enzymatic activity of MAT I/III. Among the thiol-reacting compounds belongs also free oxygen and nitrogen radicals. Indeed, hydroxyl radical, hydrogen peroxide, nitric oxide and peroxynitrite (Sánchez-Góngora et al. 1997; Avila et al. 1998) are capable to block the synthesis of SAM in liver cells by inhibition of MAT activity (Pajares et al. 2013).

Influence of essential nutrients on SAM levels and SAM-related carcinogenesis

In addition to above mentioned changes in MAT expression and activity the concentration of SAM and the flux of metabolites through SAM-cycle can be affected by mutations and/or polymorphism of the genes coding for remaining enzymatic constituents of SAM-cycle, which are participating in etiology of several cancer types (Tab. 1).

Furthermore, the levels of several essential nutrients may directly affect the flow of metabolites through SAM-cycle and SAM level (Mikol et al. 1983; Ghoshal and Farber 1984; Mentch et al. 2015) with the impact on the epigenetic changes underlying the carcinogenesis (Mehrmohamadi et al. 2016). In addition to methionine, the dietary supply of folic acid, cobalamin and pyridoxal is the solely way for sustaining their levels in human cells. The inadequate levels of those three B vitamins are linked to several diseases including cancer (Poirier et al. 2001; Selhub 2002).

Conclusion

The processes, those compromise the cellular capacity to maintain the physiological level of SAM and SAM to *S*-adenosylhomocysteine ratio, are associated with disturbed methylation of biologically important molecules and undeni-

ably are involved in etiology of several diseases. Since, altered methylation of DNA is recognized sign of cancer cells, alterations in rates of SAM cycle reactions with the impact on SAM level are considered to be significant players for a neoplastic transformation and cancer progression. Besides the genetic factors, which are affecting the metabolic operation of SAM cycle, the sufficient supply of the cells by several essential nutrients should be taken into account. Any deficiency of methionine, folic acid, B_6 and B_{12} vitamins impairs the SAM cycle and increase the risk of spontaneous tumorigenesis. In this respect, it could be supposed that SAM cycle might possess the functions of i) a checking point for balanced nutritional status and ii) an executional point in transforming the "life style" to molecular epigenetic signals. Therefore, better understanding of the processes, which are either crucial for a sustaining the appropriately operating SAM cycle or may intervene with them, might be beneficial in prediction, prevention and therapeutic approaches for several cancer types.

Acknowledgment. This work was supported by the Slovak Research and Development Agency under the contract No. APVV-0224-12. And in addition, this publication is the result of the project implementation: "Creating a new diagnostic algorithm for selected cancer diseases", ITMS code 26220220022 supported by the Operational Programme Research and Innovation funded by the ERDF. BSK was supported by Deutsche Forschungsgemeinschaft (DFG) (KO-4979/1-1).

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Received: April 21, 2017
Final version accepted: July 18, 2017