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Nutrigenomics and RNA methylation: role of micronutrients

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Abstract

RNA modifications regulate gene expression by impacting different steps in RNA processing. They are as diverse as they are important for the cell. Most of them have been identified around 1970 and the recent development of high-throughput techniques has shed some insights on their prevalence and function. They are present in all RNA types, but their regulation is still not fully understood. The most described RNA modification is methylation, which requires S-adenosylmethionine as a methyl donor, produced through the one carbon metabolism. Different micronutrients (*i.e.* folate and vitamin B12) are required to properly generate S-adenosylmethionine, making nutrition a strong regulating factor. Although micronutrients have been extensively described to affect epigenetic mechanisms such as DNA methylation, protein histone post-translational modifications or miRNAs, far less is known about RNA methylation.

Here, we review what is known about the regulation of RNA methylation by micronutrients and the physiological consequences of deficiencies.

Keywords: Epigenetics, RNA modifications, methylation, micronutrient, nutrigenomics

Abbreviations¹

¹ 2'-O-Me: 2'-O-methylation; AMPK: AMP-activated protein kinase; B12: vitamin B12; Dnmt2: DNA Methyl Transferase 2; ER: endoplasmic reticulum; FTO: Fat mass and Obesity associated protein; Hcys : Homocysteine; m¹A: N(1)-methyladenosine; m⁵C: N(5)-methylcytosine; m⁶A: N(6)-methyladenosine; m G: N(7)-methylguanosine; mCm5U: 5-carboxymethyluridine; MAT: Methionine Adenosyl Transferase; Met: Methionine; METTL3: Methyl Transferase Like 3; MS: Methionine Synthase; mt: mitochondrial; NAFLD: Non-alcoholic Fatty Liver Disease; Q: Queuosine; SAM: S-adenosylmethionine; SAH: S-adenosylhomocysteine; SNP : single nucleotide polymorphism; THF: Tetrahydrofolate; mTHF: methyl-THF; UPR: unfolded protein response; τ m⁵U: 5-taurinomethyluridine; τ m⁵(s²)U: 5-taurinomethyl-2-thiouridine.

1. Introduction

Diet and lifestyle are major determinants of chronic diseases. The so-called nutrigenomics field (how diet alters gene expression) is in full expansion, and it is now well established that food affects epigenetic modifications. Most of the studies so far have concentrated on DNA methylation, histone modifications or miRNA expression. With the recent development of high-throughput techniques, information was gained on RNA modifications, and these also appear to be affected by diet.

RNA modifications have been known for several decades now. To date, 171 of them have been reported, including methylation (the most frequent), acetylation or phosphorylation. They are listed in a database called MODOMICS [1]. These modifications are present in all RNA types (including viral RNAs): non-coding (rRNA and tRNA, the most abundant RNAs in the cell, but also snRNA or snoRNA for example...) and coding RNAs (mRNAs). These chemical modifications, which are all catalysed by various enzymes, often contribute to the local stabilization of the RNA, interactions with other molecules or to protect against degradation. For instance, modifications in tRNAs that are positioned outside the anticodon loop are generally thought to maintain structural integrity and to act as identity determinants for tRNA interacting proteins, whereas those within or proximal to the anticodon loop contribute to the fidelity and efficiency of protein synthesis [2]. However, in most cases, the function of RNA modifications remains elusive. As some of them (*i.e.* methylation of adenosine at position 6, called m⁶A) are reversible and can be modulated by environmental signals to regulate RNA function, the term “epitranscriptomics” is now used [3].

Micronutrients (vitamins and minerals) are salvaged from diet and are required in minute amounts by organisms to enable many chemical reactions as they act mostly as cofactors or co-substrates. Some of them are therefore essential for the synthesis of the chemical groups that modify RNA, especially for RNA methylation (Figure 1C), and are the subject of this minireview.

2. S-adenosylmethionine is synthesized through the one carbon metabolism

One of the most frequent and most described RNA modifications is methylation, which occurs at various positions of purines and pyrimidines. The methyl group usually originates from S-adenosylmethionine (SAM; Figure 2), which is also used to methylate DNA or proteins. The level of SAM is closely regulated by diet, as micronutrients such as vitamins B9 and B12 or betaine (named methyl donors), are essential for its synthesis (Figure 2).

The one carbon metabolism is composed of two cycles: the folate and the methionine cycle, the latter of which is also connected to glutathione synthesis (Figure 2). Importantly, it is involved in nucleotide synthesis and in amino acid metabolism. The methyl group donated by a serine is transferred to folates (or vitamin B9) and then used to produce methionine by methylating homocysteine. This step is catalyzed by methionine synthase, which requires vitamin B12 as a cofactor. This reaction is of utmost importance because hyperhomocysteinemia is a risk factor for different systemic (cardiovascular diseases) and neurologic diseases [4], [5]. Methionine is then converted by the Methionine Adenosyl Transferase (MAT) into SAM, which then transfers its methyl group to RNAs, but also to DNA, proteins, or lipids. Losing its methyl group, SAM becomes S-adenosylhomocysteine (SAH), which can then be converted into homocysteine [6]. A decrease in the level of SAM, or an alteration of the SAM/SAH *ratio*, also called the methylation index, has been associated with alterations of epigenetic and epigenomic alterations [7], [8].

3. tRNA methylation and micronutrients: an interplay known for decades

Transfer RNAs are the most heavily modified RNAs, with more than 90 unique modified nucleosides [1]. The presence of these modifications impact tRNA discrimination and translational fidelity, as well as stability or localization. Dynamic regulation of tRNA modifications modulates tRNA function, and is part of the mechanisms involved in cell response to stresses caused by environmental changes (temperature, oxidative stress or nutrient limitations, for example [9]).

Seminal observations on the impact of micronutrient deficiency on tRNA methylation originated in the late 1970's. In fact, it was reported that a deficiency in vitamin A over 7 weeks resulted in a decreased level of tRNA methyltransferases and a 5-fold decrease in the extent of the tRNA methylation in rat testis [10]. Furthermore, feeding rats with a methyl deficient (choline, methionine, folic acid and vitamin B12) diet for as little as one week resulted in liver tRNAs becoming hypomethylated [11]–[13]. Surprisingly, the activity of TRMT1 (tRNA (guanine²⁶-N²)-dimethyltransferase; EC 2.1.1.216) was increased in the liver [12-13]. Similar results on the activity of tRNA methyltransferases were obtained in carcinoma and lymphoma cell lines, as well as human embryonic fibroblasts, growing in a medium lacking methionine [14]. These data suggest that methyltransferase activity could be regulated by the SAM content in the cell. However, to our knowledge, the effect of vitamin deficiency on tRNA modifications was not investigated further, particularly regarding the molecular mechanisms involved. Hence, it has not yet been determined whether the decreased

methylation following a vitamin deficient diet is due to a direct effect (decreased level of SAM through impairment of the one carbon metabolism) or due to an indirect effect on the activity or synthesis of methyltransferases.

4. tRNA methylation and micronutrients: a cross-talk between different tRNA modifications

A decrease in some micronutrients, such as vitamins involved in the one-carbon metabolism (*i. e.* B9 or B12 vitamins), is expected to directly affect SAM levels, as they serve as coenzymes in the one-carbon metabolism, and therefore the extent of methylation on RNA substrates. Other micronutrients such as selenium, queuosine (Figure 1A) or taurine (Figure 1B), were reported to also impact tRNA methylation, *via* cross-talk between different tRNA modifications.

4.1 Selenium

Although selenium was first considered as a toxin, it is now regarded as an essential micronutrient (at low concentrations) with many health benefits, including roles in cancer and cardiovascular diseases prevention [15]. However, suboptimal selenium status was reported to be widespread in Europe and the Middle East [16]. Selenium is used for the synthesis of the 21st amino acid, selenocysteine (Sec), whose incorporation into proteins is dictated by the codon UGA [17]. Two isoacceptors of the tRNA^{[Ser]Sec} were identified, and their steady-state level and relative distribution were found to be affected by selenium, as demonstrated in cells grown in the presence of selenium or in rats fed a selenium deficient diet [18], [19]. The two isoacceptors differ by the presence of a methyl group on the 2'-O hydroxyl site of the ribosyl moiety of the 5-carboxymethyluridine present at the wobble position (mcm⁵U and mcm⁵Um; Figure 3). Selenium in the diet or in cell culture medium increases this methylation [18], thereby affecting tertiary structure. The expression of stress-related selenoproteins is dependent upon selenium and is positively correlated to the presence of mcm⁵Um [20]. Transgenic mice lacking this modification synthesize only housekeeping selenoproteins [21], [22]. A mutation in tRNA^{[Ser]Sec}, resulting in a decreased expression and 2'-O-methylation of U34, led to a reduced expression of stress-related selenoproteins, but not housekeeping proteins ([23]; Table 1). The proband suffered from symptoms ranging from abdominal pain and muscle weakness to thyroid dysfunction. Selenium supplementation may therefore prove to be a therapeutic target in this case.

4.2 Taurine and tRNA modifications

Taurine is a sulfur-containing amino acid that plays pleiotropic effects, involving modulation of calcium fluxes and neuronal excitability, osmoregulation and cell proliferation [24], [25]. Therefore, it is widely used as an ingredient in nutritional supplements. In carnivores, taurine is an essential nutrient, with little *de novo* biogenesis from cysteine. A taurine-deficient diet presents with the same manifestations as the ones found in human mitochondrial encephalomyopathies, with developmental defects, dilated cardiomyopathy and blindness due to retina failure ([26]; Table 1). In humans, infants and young children have low capacity for *de novo* synthesis of taurine from cysteine and dietary intake is therefore essential for normal development. Taurine is not found as a component of proteins but is rather incorporated to modify uridines at the anticodon wobble position (U34) to form 5-taurinomethyluridine ($\tau\text{m}^5\text{U}$; Figure 3) in mitochondrial (mt) $\text{tRNA}^{\text{Leu}(\text{UUR})}$ and tRNA^{Trp} , and 5-taurinomethyl-2-thiouridine ($\tau\text{m}^5(\text{s}^2)\text{U}$; Figure 3) in mt tRNAs for Glu, Lys and Gln [27], [28]. Mutant mt tRNAs isolated from cells of patients with mitochondrial encephalomyopathies lack taurine modification at the wobble position (reviewed in [27]). Defective taurine modification impairs mitochondrial protein synthesis by affecting codon-anticodon recognition [27].

It has been known for some time that folate deficiency could impair the respiratory chain [29], [30]. A molecular explanation was recently proposed with the finding that SHMT2, the enzyme responsible for the transfer of the methyl group from serine to tetrahydrofolate (Figure 2) in the mitochondria, provides the methyl group to produce the taurinomethyluridine base at the wobble position of some tRNAs (Figure 1B). The lack of this modified base causes defective translation, due to mitochondrial translation stalling at some lysine and leucine codons [31].

To further identify the metabolic substrates of the 5-taurinomethyl group of $\tau\text{m}^5\text{U}$ in mt tRNAs, metabolic labeling experiments using stable isotopes, coupled to LC/MS analysis, were carried out in HeLa cell culture. It was determined that extracellular taurine supplied in the medium is directly incorporated into the 5-taurinomethyl group in mt RNA [28]. Furthermore, the methylene group of $\tau\text{m}^5\text{U}$ originates from serine, with 5,10-methylene THF as an intermediate of the one carbon metabolism [32]. Cells grown in a taurine deficient medium had a reduced level of $\tau\text{m}^5(\text{s}^2)\text{U}$ and $\tau\text{m}^5\text{U}$ in mt tRNAs. Similar results were found in cats fed a control or a taurine deficient diet for 6 months, or juvenile flatfishes fed a deficient diet for 2 months ([32]; Table 1). These results show that tRNA modifications, previously regarded as static, can be modulated by sensing of the cellular metabolic status.

Even though human cells are able to synthesize taurine *de novo*, the supply coming from the extracellular environment is necessary to maintain a high frequency of modified nucleosides in the mt tRNAs.

4.3 Queuine

Cytosine-5 methylation (m^5C), described in DNA, is the paradigm of epigenetic modifications. It is also present in tRNAs, and m^5C methylation at position C38 (Figure 3) is driven by the Dnmt2 (DNA Methyl Transferase 2) family of methyltransferases [33], the most common substrate being $tRNA^{Asp}$ [34]. Activity of the fission yeast homolog of Dnmt2, named Pmt1, was shown to be regulated by nutritional cues [33] which were later identified as queuine (Figure 1A; [35]). This micronutrient, salvaged from diet and gut microbiota, enables the formation of queuosine, a modification found at the wobble position of the anticodon loop of the tRNA [36]. Replacement of guanosine by queuosine (Q) was proposed to alter mRNA codon recognition, to affect proper protein synthesis and to control translational speed [37]. Its depletion activates cellular stress responses *in vitro* and *in vivo* [38]. Q tRNAs are often hypomodified in transformed cells, and Q deficiency is linked to various kinds of tumors [39].

The difficulty of working with germ-free mice or to obtain a queuine deficient diet has long precluded the study of this micronutrient in metazoan. Recently, using mammalian cells cultured with a synthetic serum-free medium thereby devoid of queuine, Tuorto and colleagues showed that queuine modification promotes C38 methylation [38] (Figure 3; Table 1). Lack of queuine modification resulted in less methylation of $tRNA^{Asp}$ and a reduced translational speed at decoded and near-cognate codons. Cells grown in queuine deficient medium showed an increase in endoplasmic reticulum (ER) stress and the unfolded protein response (UPR). Similar results were obtained in liver of axenic mice fed a queuine deficient diet for 2 months. Along with a reduced level of Q-tRNA and a lower level of m^5C at position 38, the UPR, ER and oxidative stress pathways were deregulated [38].

5. Methylation in mRNAs: a still uncharted territory

It is important to note that less abundant RNAs are also modified by methylation. Out of the few internal modifications found in mRNAs, m^6A was the first to be identified [40]. As well, it is the most abundant modification, and is currently the most studied. The other modifications (m^7G (N(7)-methylguanosine), 2'-O-methylation, or the controversial m^5C and m^1A (N(1)-methyladenosine)) are less understood in terms of function or identity of the

writers/readers/erasers. Following the recognition of the importance of these mRNA modifications, the term epitranscriptome is now used, and this field is in full expansion. Indeed, akin to DNA methylation, these modifications seem to be dynamic and require writers, readers and erasers. In the case of m⁶A, its level varies across tissues and developmental stages [41], as well as the nutrient status [42], [43]. Indeed, the fat mass and obesity associated protein (FTO) was identified as a Fe²⁺/2-oxoglutarate dependent demethylase, preferentially catalyzing m⁶A removal in RNA [44], [45]. This protein plays a key role in metabolic diseases [46] and SNPs (single nucleotide polymorphism) in the first intron of the *FTO* gene were found to be strongly associated with increased body mass index, and an increased risk of childhood and adult obesity [47], [48]. In fact, subjects homozygous for the high-risk allele exhibit increased *ad libitum* food intake and for children, obesity-prone eating behaviors. FTO transgenic mice support its role in regulating body weight, as overexpression results in obesity, whereas null or mutant mice display a lean phenotype [49]. Several reports have shown that diet (restriction, high fat or high glucose diet) affects m⁶A levels by affecting FTO or Methyl Transferase Like 3 protein (METTL3), which contains the catalytic activity responsible for m⁶A formation. It was also reported that fasting induces an increase of FTO mRNA and protein expression in the hypothalamus of rats [50]. Furthermore, FTO was mislocalized in the cytoplasm of some neurons due to an altered phosphorylation pattern.

Importantly, FTO is also involved in non-alcoholic fatty liver disease (NAFLD), the most common cause of chronic liver disease in the developed world. The hepatoprotective effects of betaine (Figure 2; Table 1) were reported in animal models of NAFLD [51], [52]. Because betaine is used to synthesize SAM, it is thought to modulate gene expression through epigenetic marks. Chen et al. reported that betaine supplementation prevented the increase of triglyceride, AST and ALT levels in the serum, in a rat model of NAFLD induced by a 6 week high-fat diet [53]. Upon betaine supplementation, SAM level in the liver was restored, resulting in more m⁶A levels and a reduced expression of FTO [53]. Similar results were found in the adipose tissue of mice fed a high-fat diet for 8 weeks. Supplementation with betaine reversed the effects on m⁶A levels and the altered expression of fatty acid oxidation or lipolysis related genes caused by the diet [54]. The mechanism seems to involve AMPK (AMP-activated protein kinase) as in *Ampk*^{-/-} knock-out mice, betaine had no counteracting effect. However, the precise mechanisms and a direct role of betaine on mRNA methylation remain to be uncovered.

6. Conclusions and future directions

Micronutrients are not produced by the human body and must be acquired from food. Although required in only minute amounts, deficiencies in micronutrients can have devastating effects on the health of children during development, adults, and the elderly. Globally, more than 2 billion people suffer from one or more micronutrient deficiency, including at least half of children worldwide ages 6 months to 5 years. Increasing evidence suggests that micronutrient deficiency can alter gene expression at the epigenetic level, with DNA methylation, histone modifications and miRNA expression being mostly described. Far less concern has been devoted to RNA modifications, even if the field of epitranscriptomics has gained much interest in the past few years. Most RNA methylases use SAM as the methyl group donor. It was recently reported that the level of MAT2A (the SAM synthetase, Figure 2) is regulated through m⁶A modification within specific hairpin structures in the 3'-UTR upon methionine depletion in the cell culture medium, promoting splicing of an otherwise retained intron [54], [55]. Another mechanism requires the reader protein YTHDC1 to mediate down-regulation of the MAT2A mRNA under high SAM conditions [55]. The methylation reaction is not catalysed by METTL3 as in most cases, but rather by METTL16. This finding of a feed-back loop highlights the importance of precisely regulated SAM levels. The one carbon metabolism is also dependent on the presence of micronutrients, such as B9 and B12 vitamins. Deficiency in these vitamins is frequent in pregnant women and in elderly people, and is linked to an increased risk of neurodevelopmental defects during gestation, or to neurodegenerative disorders or cardiovascular diseases later in life [7]. Inappropriate intake of micronutrients necessary for SAM production is therefore likely to impact methylation modifications in different classes of RNA. Up to now, tRNAs have been the most described, but the recent identification of several internal methylated residues in mRNA open a whole new area of research.

Taken together, those data suggest that RNA methylations are very important for RNA processing and cell metabolism. A perturbation of epigenetic modifications caused by a diet deficient in micronutrients, such as queuine or B vitamins, can lead to pathological consequences for the cell and/or the organism. Therefore, adequate food intake, particularly micronutrients (compared to the macronutrients carbohydrates, fat and proteins) is mandatory to ensure a proper epitranscriptomic regulation of RNA expression.

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8. Declaration of interest

None.

9. Author contributions

PM, BL and ND wrote and edited the manuscript.

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11. Table 1

Modification	Diet	Experimental model	Effect	Disease	Reference
Υm^5U	Taurine deficiency 6 months Taurine deficiency 2 months	Cat flatfish	reduced frequency	developmental defects, blindness, cardiomyopathy	[32]
Υm^5U $\Upsilon m^5(s^2)U$		genetic disease with mutation in tRNA Leu ^{UUR} /tRNA Lys	reduced respiratory activity	MELAS, MERFF	[28]
mcm ⁵ U/mcm ⁵ Um	2 week deficiency 4 month deficient diet	human cells rat	affect both the steady-state level and distribution of 2 tRNA[Ser]Sec		[19]
Queuosine m ⁵ C C38	queuine deficient diet 2 months queuine deficient medium	mouse human cells	activation of UPR and ER stress oxidative stress		[38]
m ⁶ A	high-fat diet w/wo betaine supplementation betaine treatment	rat transgenic mice knock-out for AMPK1 primary adipocytes	increased m ⁶ A, reduced triglyceride accumulation in the liver increased m ⁶ A, reduced triglyceride accumulation in adipose tissue increased m ⁶ A, reduced triglyceride accumulation	NAFLD NAFLD	[53] [54]

12. Figure legends

Figure 1: Examples of RNA modifications with chemical groups donated by micronutrients

A Queuine is salvaged from food and gut microbiota. It is used to modify guanine at the wobble position to form queuosine.

B Taurine is found in maternal milk and food from animal origin. It modifies uridine at the wobble position of the tRNA.

C S-adenosylmethionine (SAM) synthesis is regulated by vitamins B9 and B12, which are found in vegetables and food of animal origin, respectively. The methyl group is used to methylate different nucleotides, the most prevalent in mRNA being N6-methyladenosine (m⁶A). Cytosines are also methylated, like in DNA (m⁵C).

Figure 2: The one carbon metabolism

Vitamin B12 (B12) is the cofactor of methionine synthase (MS). It enables the transfer of the methyl group from a folate to the methionine (Met). Met is the S-adenosylmethionine (SAM) precursor. The loss of the methyl group from SAM (used for transmethylation reactions of various substrates such as DNA, proteins, or RNA) gives S-adenosylhomocysteine (SAH), which is further converted into homocysteine (Hcys). Ser: Serine, Gly: glycine THF: tetrahydrofolate, mTHF: methyltetrahydrofolate, MAT: methionine adenosyl transferase, DMG: dimethylglycine, SHMT : serine hydroxymethyltransferase.

Figure 3: tRNA modifications

tRNA are composed of an acceptor stem (yellow), a D loop (green), a A loop (blue), a variable loop (pink) and a T loop (grey). Codons recognize the anticodon (red) composed of nucleotides that can be modified depending on micronutrient deficiencies.

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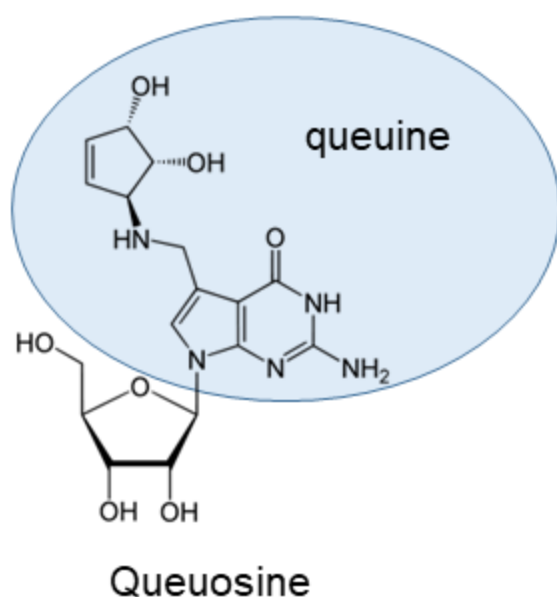
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Figure 1

A
Food, gut microbiota



B
Maternal milk, fish, meat
poultry

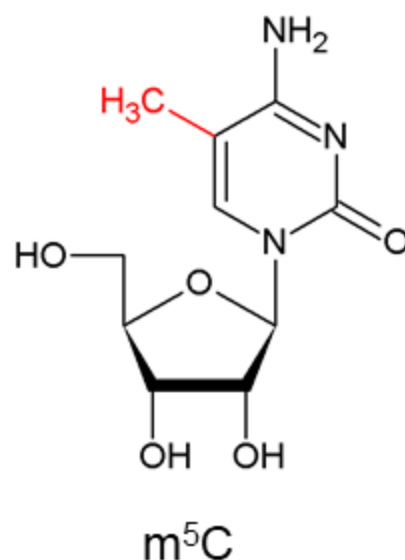
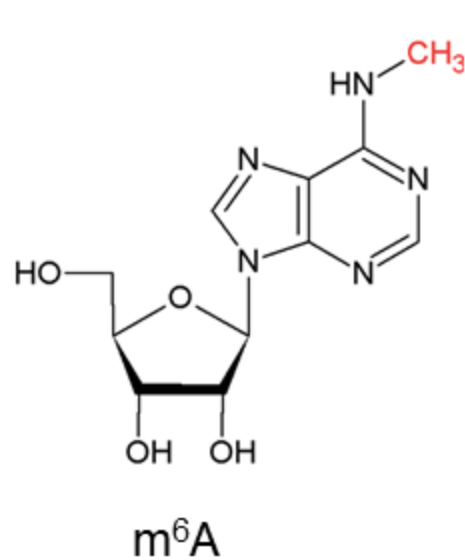
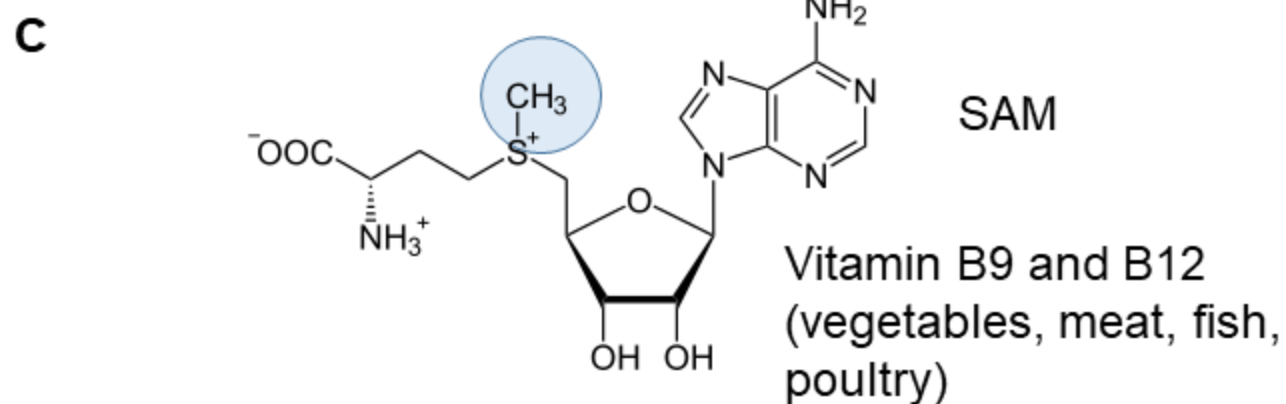
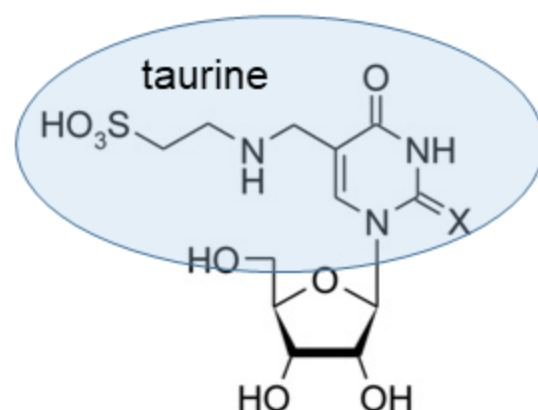


Figure 2

