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Biotin and biotinidase deficiency

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Abstract

Biotin is a water-soluble vitamin that serves as an essential coenzyme for five carboxylases in mammals. Biotin-dependent carboxylases catalyze the fixation of bicarbonate in organic acids and play crucial roles in the metabolism of fatty acids, amino acids and glucose. Carboxylase activities decrease substantially in response to biotin deficiency. Biotin is also covalently attached to histones; biotinylated histones are enriched in repeat regions in the human genome and appear to play a role in transcriptional repression of genes and genome stability. Biotin deficiency may be caused by insufficient dietary uptake of biotin, drug–vitamin interactions and, perhaps, by increased biotin catabolism during pregnancy and in smokers. Biotin deficiency can also be precipitated by decreased activities of the following proteins that play critical roles in biotin homeostasis: the vitamin transporters sodium-dependent multivitamin transporter and monocarboxylate transporter 1, which mediate biotin transport in the intestine, liver and peripheral tissues, and renal reabsorption; holocarboxylase synthetase, which mediates the binding of biotin to carboxylases and histones; and biotinidase, which plays a central role in the intestinal absorption of biotin, the transport of biotin in plasma and the regulation of histone biotinylation. Symptoms of biotin deficiency include seizures, hypotonia, ataxia, dermatitis, hair loss, mental retardation, ketolactic acidosis, organic aciduria and also fetal malformations. This review focuses on the deficiencies of both biotin and biotinidase, and the medical management of such cases.

Keywords

biotin; biotinidase; carboxylases; deficiency; histones; holocarboxylase synthetase

Biotin

Biotin is an essential water-soluble vitamin and the adequate intake (AI) for adults is 30 μg/day [1]. Biotin serves as a coenzyme for acetyl-CoA carboxylases (ACC)α and ACCβ, propionyl-CoA carboxylase (PCC), 3-methylcrotonyl-CoA carboxylase (MCC) and pyruvate carboxylase (PC); biotin is covalently bound to the ε-amino group of a specific lysine residue in carboxylases [2]. The biotin-dependent carboxylases catalyze pathways involved in fatty

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acid biosynthesis, gluconeogenesis, tricarboxylic acid cycle anaplerosis and pleiotropic gene regulation, particularly for genes in carbohydrate metabolism. ACCα, the only human carboxylase to reside in the cytoplasm [2,3], catalyzes the binding of bicarbonate to acetyl-CoA, generating malonyl-CoA for fatty acid synthesis [2,3]. ACCβ, PCC, MCC and PC are located in the mitochondrial matrix. ACCβ participates in the regulation of fatty acid oxidation and might also serve as a reservoir for biotin [3,4]. PCC and MCC each comprise of biotin-containing α-subunits and biotin-free β-subunits [2]. PCC catalyzes essential steps in the metabolism of amino acids, cholesterol and odd-chain fatty acids [2], and MCC catalyzes an essential step in leucine metabolism. PC catalyzes an essential step in gluconeogenesis [2] and also plays important roles in lipogenesis [5,6], glucose-induced insulin release [7] and tricarboxylic acid anaplerosis [8]. Therefore, biotin homeostasis is crucial for maintaining normal body functions, in particular, in the heart muscle and brain [8,9]. Biotin homeostasis is achieved by efficient, transporter-mediated intestinal absorption and cellular transport of biotin by enzyme-mediated conjugation of biotin to carboxylases, and by an efficient recycling mechanism that minimizes the urinary excretion of biotin.

The following three proteins play major roles in the homeostasis of biotin (Figure 1): biotinidase (BTD), the sodium-dependent multivitamin transporter (SMVT) and holocarboxylase synthetase (HCS). Dietary biotin exists in free and protein-bound forms [10]. Gastrointestinal proteases and peptidases digest biotin-containing proteins to release biocytin (biotinyl-ε-lysine) and biotin-containing peptides [11]. BTD is secreted in pancreatic fluids and plays a critical role in releasing free biotin from biocytin and biotinylated peptides prior to absorption. Intestinal BTD may also be derived from the intestinal flora, intestinal secretions and brushborder membranes [11,12].

The SMVT is responsible for intestinal absorption of free biotin, renal reabsorption and transport across cell membranes in liver and peripheral tissues [13–15]. In lymphoid cells, the monocarboxylate transporter 1 might also contribute to biotin uptake [16]. BTD is secreted in large quantities into blood plasma and participates in the transport of biotin to peripheral tissues [11].

The attachment of biotin to lysine residues in carboxylases and histones (see later) is catalyzed by HCS [17–19]. Biotin-dependent carboxylases have half-lives of 1–8 days [20–25]. Degradation of holocarboxylases leads to the release of biocytin and biotinylated peptides. BTD catalyzes the release of free biotin from these breakdown products for recycling in holocarboxylase synthesis. Taken together, BTD plays a fundamental role in biotin homeostasis and, therefore, is the focus of this review article.

Biotin deficiency

Mock and coworkers provided evidence that approximately half of the pregnant women in the USA are marginally biotin-deficient, despite a normal dietary biotin intake [26–28]. These claims are based on comparisons of well-known markers of biotin status in pregnant women to those in nonpregnant women (e.g., the urinary excretion of 3-hydroxyisovaleric acid and biotin) and the activity of propionyl-CoA carboxylase in lymphocytes. If there was a link between marginal biotin deficiency and fetal malformations in humans, the findings by Mock and coworkers would have important implications for health policies and intake recommendations. Currently, this link is somewhat uncertain. While animal studies have clearly demonstrated that biotin deficiency is teratogenic, the severity of deficiency in these animal studies typically exceeded what was observed in pregnant women. Notwithstanding these limitations, the teratogenic effects of biotin deficiency in animal models are striking and deserve a brief summary [29–31]. For example, hens with biotin deficiency produce eggs with higher embryonic mortality, reduced hatchability and malformations such as chronodystrophy,

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perosis, micromelia and syndactyly [31]. In some strains of mice, biotin deficiency during pregnancy causes substantial increases in fetal malformations and mortality [30,31]. The most common fetal malformations in biotin-deficient rats include cleft palate, micrognathia and micromelia. Differences in teratogenic susceptibility among rodent species have been reported and corresponding differences of biotin concentrations in fetal liver were observed. This led Watanabe and coworkers to propose that differences in teratogenic susceptibility among rodent species are caused by differences in biotin transport from the mother to the fetus [32]. Evidence has been provided that biotin catabolism to bisnorbiotin is increased in pregnant women compared with nonpregnant controls [26,33]. The fetal-to-maternal concentration ratio of biotin plus metabolites is approximately 6:1, suggesting that fetal biotin accumulation might contribute to maternal biotin depletion [34]. However, Mock and coworkers reported that the activity of PCC is reduced by approximately 90% in the fetus at term in response to feeding an egg white that causes only a 50% reduction in maternal hepatic PCC activity [35]. They speculated that this finding indicates that the fetus may not really be an efficient biotin parasite, in contrast to most other micronutrients.

Biotin deficiency has also been reported in individuals who are treated with anticonvulsants [36,37]. Other potential causes of biotin deficiency are intestinal malabsorption in individuals with short bowel syndrome, long-term use of drugs such as antibiotics, certain antiseizure medications and lipoic acid, excessive alcohol consumption and continuous consumption of raw egg white [38–43]. Raw egg white contains the protein avidin, which binds biotin tightly, rendering it unavailable for absorption [38,44]. Recent studies show that smoking accelerates biotin catabolism, especially in women, resulting in marginal biotin deficiency [45]. Biotin-deficient human fibroblasts undergo senescence earlier than their biotin-sufficient controls [46]. These biotin-deficient cells selectively lost mitochondrial complex IV that was associated with decreased heme synthesis. Moreover, biotin-deficient cells exhibited an increased susceptibility to oxidative damage in response to stress. Importantly, biotin deficiency has been reported in severely malnourished children [47], creating a global public-health problem [48].

BTD deficiency

Biotin deficiency may also be caused by a deficiency of the three proteins involved in biotin homeostasis: HCS, BTD and SMVT [18,49–53]. This review will not discuss SMVT and HCS, only BTD, because of its central role in biotin recycling and transport, as discussed previously. BTD deficiency can result from gene mutations, including deletions, insertions, cryptic splice site formation, single nucleotide insertion and deletion, and point mutations [54]. Mutations of the *BTD* gene have been well characterized at the molecular level [54–57] and are discussed later.

Deficiency of BTD leads to failure in releasing biotin from dietary proteins, thereby decreasing bioavailability. In addition, the urinary excretion of biotin might increase due to increased renal filtration of free biotin (lack of the biotin transport protein BTD), and impaired recycling of biotin from breakdown products of biotinylated carboxylases, such as biocytin [58–60]. Impaired serum BTD activity, together with increased biotin requirements, have also been reported in patients suffering from chronic liver diseases, such as cirrhosis [61]. Clinical and biochemical features in patients with BTD deficiency are similar to those of biotin and HCS deficiency, but not limited to those described for biotin deficiency [62,63], suggesting the existence of additional unknown activities of BTD. These BTD deficiency clinical features include hearing loss and optic atrophy in addition to the common biotin deficiency symptoms, such as seizures, hypotonia, ataxia, dermatitis, hair loss, mental retardation, ketolactic acidosis and organic aciduria [59,63–67].

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Typically, findings of BTD deficiency appear at age 1 week to more than 1 year [62]. Profound BTD deficiency is characterized by less than 10% of normal serum BTD activity, whereas patients with partial deficiency possess 10–30% of normal BTD activity [68]. The estimated incidence of profound BTD deficiency is one in 112,271 and the incidence of partial BTD deficiency is one in 129,282 [68]. The combined incidence of profound and partial deficiency is one in 60,089 live births; an estimated one in 123 individuals is heterozygous for the disorder [68]. Most of the children in whom BTD deficiency has been diagnosed are Caucasian [62]. BTD-deficient patients are typically treated with lifelong daily doses of biotin 5–20 mg to compensate for decreased bioavailability from food sources and increased urinary losses [62, 68].

Failure to diagnose and treat BTD deficiency at an early stage may cause irreversible neurological damage, leading to developmental delay and autistic behavior [51,69,70]. This could be attributed to an increased vulnerability of the brain to biotin deficiency. Symptomatic patients improve rapidly if biotin therapy is initiated early; hence the prognosis of BTD deficiency is favored by early institution of biotin therapy during infancy or childhood. Biotin therapy must be continued throughout life [62,70].

Pathogenesis of BTD, HCS and biotin deficiency are similar, and multiple carboxylase deficiency is characterized by low activities of ACC, MCC, PC and PCC. BTD deficiency can be unambiguously diagnosed by using a fairly easy colorimetric assay for BTD activity in cultured amniotic fluid cells or neonatal blood samples [62]. BTD activity is measured by quantitating the release of *p*-aminobenzoic acid from *N*-biotinyl-*p*-aminobenzoate [71]. The mean (± standard deviation [SD]) normal activity of BTD is 5.8 ± 0.9 nmol *p*-aminobenzoate liberated $min^{-1} \cdot ml^{-1}$ serum [71].

BTD gene

Biotinidase belongs to the nitrilase superfamily of enzymes, which consists of 12 families of amidases, *N*-acyltransferases and nitrilases [72]. Some members of the nitrilase superfamily (vanins-1, -2 and -3) share significant sequence similarities with BTD [73]; it is unknown whether vanins use histones as acceptor molecules in transferase reactions (see later). Human *BTD* gene has been cloned, sequenced and characterized [74]. The gene localizes to human chromosome 3p25. The structure of the human *BTD* gene has been determined [75]; the 5′-flanking region of exon 1 contains a CCAAT element, three initiator sequences, an octamer sequence, three methylation consensus sites, two GC boxes and one hepatocyte nuclear factor (HNF)-5 site, but has no TATA element. The organization of the *BTD* gene reveals features of a CpG island and resembles a housekeeping gene promoter in region −600 to +400 relative to the transcription start site. The human *BTD* gene contains four exons, which span at least 44 kb and encode a protein of 543 amino acids [76]. The four exons have been designated $A_{-125-44}$, B_{45-309}, $C_{310-459}$ and $D_{460-1961}$. The mature enzyme is encoded by exons B through D. The coding region of BTD has two in-frame start codons, both of which might initiate translation. Recently, three alternatively spliced variants of BTD have been identified in multiple human tissues: alternative splicing occurs in exon A (exon 1) and the three variants were designated 1a, 1b and 1c [76,77].

The cellular distribution of BTD is controversial. While the existence of BTD acitivty in microsomes and mitochondria is accepted universally [78–80], the presence of BTD in nuclei is less certain. Pispa proposed that 26% of the cellular BTD activity is located in the nuclear fraction [80], which was confirmed by subsequent immunocytochemistry studies [81]. No nuclear BTD was detected by Stanley *et al.* [76]. Alternative splicing of BTD might play a role in regulating its subcellular localization and tissue specificity [76]. For example, the 1c variant can only be detected in the testes [76]. Mature BTD (85 kDa) has been detected in microsomes

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and lysosomes, whereas a 48-kDa BTD variant was detected in mitochondria [76]. The 85-kDa protein possesses full biotinyl-hydrolase and transferase abilities, whereas the 48-kDa variant lacks those activities [76]. It cannot formally be excluded that the 48-kDa protein is an artifact produced by protein breakdown during sample preparation.

The structure of the BTD protein has not yet been characterized in great detail, primarily due to the absence of crystallography data. The expression and purification of bioactive BTD has proven to be difficult [82]. This obstacle has been partially by-passed by using *in silico* modeling to predict the 3D structure of BTD [82]. This model is based on crystallography data from prokaryotic nitrilase and amidase domains. The BTD model predicts a protein with two major domains. Using sequence comparisons among mammals and *Drosophila*, a 62-amino acid conserved region was identified that probably harbors the active site of BTD [83]. Highly conserved glutamate, lysine and cysteine residues (Glu112, Lysine212 and Cys245) were also identified [82]. Using the *in silico* model, Pindolia *et al.* characterized 45 missense mutations known to affect BTD activity [82]. Finally, the model predicts the existence of multiple disulfide bonds needed for enzyme stability and correct folding in addition to six glycosylation sites located on the surface of BTD that might also be involved in the enzyme function, secretion into the extracellular space and cellular localization. These model predictions are consistent with previous observations in disulfide bond formation and glycosylation of BTD [76]. The controversial roles of BTD in the biotinylation and debiotinylation of histones are discussed later.

More than 110 BTD mutations have been reported that decrease BTD activity (Online Mendelian Inheritance in Man [OMIM] accession #609019), leading to multiple carboxylase deficiency as described previously [201]. This field of research has been pioneered by Wolf and coworkers [54,77,84–86]. Both early-onset (neonatal) and late-onset (juvenile) forms of BTD deficiency have been reported [87]. It has been speculated that the early-onset forms of BTD deficiency (multiple carboxylase deficiency) might be caused by mutations in the *BTD* gene, whereas the late-onset forms might be caused by decreased secretion of BTD into the intestinal lumen [88].

Research by Wolf and coworkers identified a number of mutations in the *BTD* gene that account for most of the observed cases of BTD deficiency. For example, 50% of symptomatic children have a 7-bp deletion coupled with a 3-bp insertion in at least one of their alleles of the *BTD* gene or a substitution that corresponds to a R538C change [77]. Other aberrations include a deletion/insertion mutation in exon $D_{460–1961}$ that causes a frame shift and premature termination and the translation of a truncated protein [77]. Recently, Wolf *et al.* reported 17 novel mutations that cause profound BTD deficiency [85]. Six of the reported mutations are due to deletions, whereas the remaining 11 mutations are missense mutations located throughout the gene, and encode amino acids that are conserved in mammals. Hymes *et al.* reported 61 mutations that take place in three of the four exons of the *BTD* gene and one mutation in an intron associated with profound BTD deficiency [54]. Finally, Muhl *et al.* analyzed samples from 21 patients with profound BTD deficiency and 13 patients with partial BTD deficiency [89]. Of the cases of partial BTD deficiency, the D444H mutation was the dominant mutation, accounting for 92% of cases.

Histone biotinylation

Chromatin & gene regulation

Chromatin comprises DNA and DNA-binding proteins (i.e., histones and nonhistone proteins). Histones play a predominant role in the folding of DNA into chromatin [90]. Five major classes of histones have been identified in mammals: H1, H2A, H2B, H3 and H4. Histones consist of a globular domain and a more flexible amino terminus (histone ‘tail’). DNA and histones form

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repetitive nucleoprotein units, the nucleosomes [90]. Each nucleosome (nucleosomal core particle) consists of 147 bps of DNA wrapped around an octamer of core histones (one H3–H3–H4–H4 tetramer and two H2A–H2B dimers). One molecule of histone H1 is positioned on top of each nucleosome, binding to the linker DNA region between the histone beads.

The amino terminal tail of histones protrudes from the nucleosomal surface; covalent modifications of this tail affect the structure of chromatin and form the basis for gene regulation [91–96]. Amino acid residues in histone tails are modified by covalent acetylation [97–99], methylation [90], phosphorylation [90], ubiquitination [90] and poly (ADP-ribosylation) (Figure 2) [100–102]. The various modifications of histones have distinct functions. For example, trimethylation of K4 in histone H3 is associated with transcriptional activation of surrounding DNA, whereas dimethylation of K9 is associated with transcriptional silencing [95,103]. Covalent modifications of histones are reversible [95].

Histone biotinylation

The classical role of biotin is to serve as a covalently bound coenzyme for five carboxylases (see previously); biotinylation of carboxylases is catalyzed by HCS [2]. Recently, we provided evidence that biotin is also linked to histones (DNA-binding proteins) via an amide bond [104]. In previous studies, we identified eleven distinct biotinylation sites in histones H2A, H3 and H4 (Figure 2) and generated site-specific antibodies to these biotinylated histones [105–108]. Bailey *et al.* proposed that streptavidin (a classical probe for biotin) binds to histones independently of biotin and cautioned against the use of streptavidin when probing biotinylated histones [109]. These studies make a case for using biotinylation site-specific antibodies in chromatin studies.

Functions of histone biotinylation in chromatin remodeling are emerging. For example, biotinylation of K12 in histone H4 plays roles in gene repression, DNA repair, heterochromatin structures and repression of transposons to mediate genomic stability and minimize cancer risk in human cells and *Drosophila melanogaster* [19,110–113]. Importantly, biotinylation of histones depends on biotin supply [114,115] and, therefore, might be decreased in BTD-deficient patients where biotin recycling is impaired [19,111]. It is unknown what percentage of lysine residues in histones is biotinylated. Studies in telomeric repeats provided evidence that approximately one out of three molecules of histone H4 is biotinylated at K12 in this region (Wijeratne SSK, Unpublished Obsevation). Less than 1% of total cellular biotin localizes to the cell nucleus [104].

Initially, it was proposed that BTD mediates biotinylation of histones. Hymes *et al.* have proposed a reaction mechanism by which cleavage of biocytin (biotin-ε-lysine) by BTD leads to the formation of a biotinyl-thioester intermediate (cysteine-bound biotin) at or near the active site of BTD [59,116]. In a next step, the biotinyl moiety is transferred from the thioester to the ε-amino group of lysine in histones. The substrate (biocytin) for biotinylation of histones is generated in the breakdown of biotin-dependent carboxylases, which contain biotin linked to the ε-amino group of a lysine moiety [62,80].

Recently, Narang *et al.* provided evidence that HCS can also biotinylate histones [18]. Notwithstanding the ability of BTD to catalyze biotinylation of histones, studies by Camporeale *et al.* suggest that HCS is more important than BTD for biotinylation of histones [19]. Importantly, knockdown of HCS and BTD decrease histone biotinylation, cause abnormal gene expression patterns and phenotypes such as decreased life span and heat resistance in *D. melanogaster* [19]. Effects of BTD knockdown can probably be attributed to a secondary biotin deficiency due to impaired biotin recycling.

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Debiotinylation of histones

Biotinylation of histones is a reversible modification, but the mechanisms mediating debiotinylation of histones are largely unknown. Recent studies suggest that BTD may catalyze both biotinylation and debiotinylation of histones [117]. Variables such as the microenvironment in chromatin, post-translational modifications and alternate splicing of BTD might determine whether BTD acts as biotinyl histone transferase or histone debiotinylase. This assumption is based on the following lines of reasoning. First, the availability of substrate might favor either biotinylation or debiotinylation of histones. For example, locally high concentrations of biocytin might increase the rate of histone biotinylation in confined regions of chromatin. Note that the pH is unlikely to affect the biotinylation equilibrium, given that the pH optimum is similar (pH 8) for both the biotinylating activity [116] and the debiotinylating activity of BTD [117]. Second, proteins may interact with BTD at the chromatin level, favoring either biotinylation or debiotinylation of histones. Third, three alternatively spliced variants of BTD have been identified [76]. Theoretically, these variants may have unique functions in histone metabolism. Fourth, some variants of BTD are modified post-translationally by glycosylation [74,76], potentially affecting enzymatic activity. An assay for analysis of histone debiotinylases is available [81].

Synthetic BTD inhibitors & analytical tools

BTD inhibitors

Classical studies of biotin metabolism proposed using biotin, di-isopropylfluorophosphate and thiol reagents, such as *p*-chloromercuribenzoate, as inhibitors of BTD *in vitro* [80]. By today's standards, these compounds are of limited use for the following two reasons. First, di-isopropylfluorophosphate and *p*-chloromercuribenzoate are general inhibitors of enzymes as opposed to being specific inhibitors of BTD. Second, simultaneous inhibition of BTD in both cytoplasm and the nucleus make it impossible to link potential effects of low BTD activity to altered histone debiotinylation in the nucleus as opposed to impaired biotin recycling in the cytoplasm. Recently, Kobza *et al.* identified synthetic biotin analogs that specifically inhibit BTD [107]. The following compounds inhibited BTD activity by 26–80% if used at a concentration of 1 mmol/l: biotinyl anilide, biotinyl allylamide, biotinyl *N*-methylanilide, biotinyl-methyl 4-(amidomethyl) benzoate, biotinyl 2-amido-pyridine, biotinyl 4-amidophenylboronic acid and biotinyl benzylamide. Biotinyl-methyl 4-(amidomethyl) benzoate was the most effective compound of all the inhibitors tested. Enzyme kinetics studies were consistent with the hypothesis that these compounds acted by competitive inhibition of BTD. Biotinyl-methyl 4-(amidomethyl) benzoate did not affect biotin transport in human cells, suggesting specificity in regard to biotin-related processes. The development of these inhibitors is an important first step towards the generation of BTD-specific and cell compartment-specific inhibitors. Second-generation inhibitors will need to be designed to prevent hydrolytic cleavage of amide bonds in biotin analogs and to target inhibitors to specific cellular compartments (e.g., nuclei).

Analytical tools

Kobza *et al.* adopted an existing colorimetric BTD assay for use in a novel 96-well plate format to permit high-throughput screening of potential BTD inhibitors [107]. Antibodies to BTD are available [105].

Expert commentary

The importance of biotin for human health has been under-appreciated for many years. Health professionals thought that the role of biotin in human well-being was limited to that as a coenzyme for carboxylases and that biotin deficiency was fairly rare in free-living humans.

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This view has changed considerably over the past few years. Evidence has been provided that marginal biotin deficiency might be more common than widely believed, particularly in certain subgroups of the general population, such as pregnant women, patients treated with certain drugs and severely malnourished children. The significance of biotin deficiency in humans has been underlined by observations that biotin deficiency is teratogenic in some animal species. A link between marginal biotin deficiency in pregnant women and the incidence of birth defects has yet to be established. Similarly, it will be important to validate cut-off points to define biotin deficiency in pregnant women. Importantly, it is now clear that biotin plays a role in chromatin structure, mediated by its binding to distinct lysine residues in several classes of histones. Abnormally low biotinylation of histones appears to impair gene repression and repression of transposable elements, thereby decreasing genome stability. Here, too, there is plenty of opportunity for future research with a potentially great relevance for human health. For example, it is currently unknown how enzymes that mediate biotinylation of histones are being targeted to distinct regions in human chromatin. Similarly, the mechanisms of gene repression by histone biotinylation have not yet been established. Finally, while it has been proposed that BTD acts as a histone debiotinylase, no unambiguous evidence for such a role has yet been provided. Health professionals are encouraged to keep up-to-date with the exciting new findings made in the biotin field because of the significance of this vitamin for human health. Similarly, researchers are encouraged to engage in biotin research because of the great opportunities offered by the recent developments in this field.

Five-year view

Undoubtedly, a bulk of new information will emerge with regard to structures, functions and mutations of HCS and BTD owing to the importance of these enzymes in biotin homeostasis and chromatin structure. Structural analyses are already underway in a few select laboratories. Identification of novel histone biotinylation sites and characterization of their biological functions is just a matter of time. While the mechanism of action of histone biotinylation in mediating gene regulation might remain obscure for a few more years, one might speculate that RNAi might play an important role. Future research will probably characterize links between histone biotinylation and DNA methylation and, perhaps, other epigenetic phenomena. The roles of biotin in chromatin structure will also probably offer explanations for why biotin deficiency causes fetal malformations. In that context, it is anticipated that biotin requirements and homeostasis in pregnant women and their fetuses will be much clearer defined during the course of the next 5 years.

Key Issues

- Biotin is a water-soluble vitamin that serves as a coenzyme for five carboxylases in humans. Carboxylases play essential roles in macronutrient metabolism.
- Biotin is also covalently attached to histones. Biotinylation of histones plays a role in gene repression and repression of transposable elements, thereby maintaining genome stability.
- Biotin homeostasis is maintained by dietary intake, the biotin transporters monocarboxylate transporter 1 and sodium-dependent multivitamin transporter, the biotin protein ligase holocarboxylase synthetase and the biotin peptidyl hydrolase biotinidase (BTD).
- Evidence has been provided that approximately 50% of pregnant women are marginally biotin deficient and that severe biotin deficiency is teratogenic in some animals. Biotin status is impaired by interactions with some drugs and in severely malnourished children.

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- BTD plays multiple roles in biotin metabolism (i.e., intestinal release of free biotin and plasma transport) and the recycling of biotin from breakdown products of biotinylated carboxylases.
- The exact role of BTD in the regulation of histone biotinylation is uncertain.
- More than 110 mutations have been identified in the *BTD* gene.

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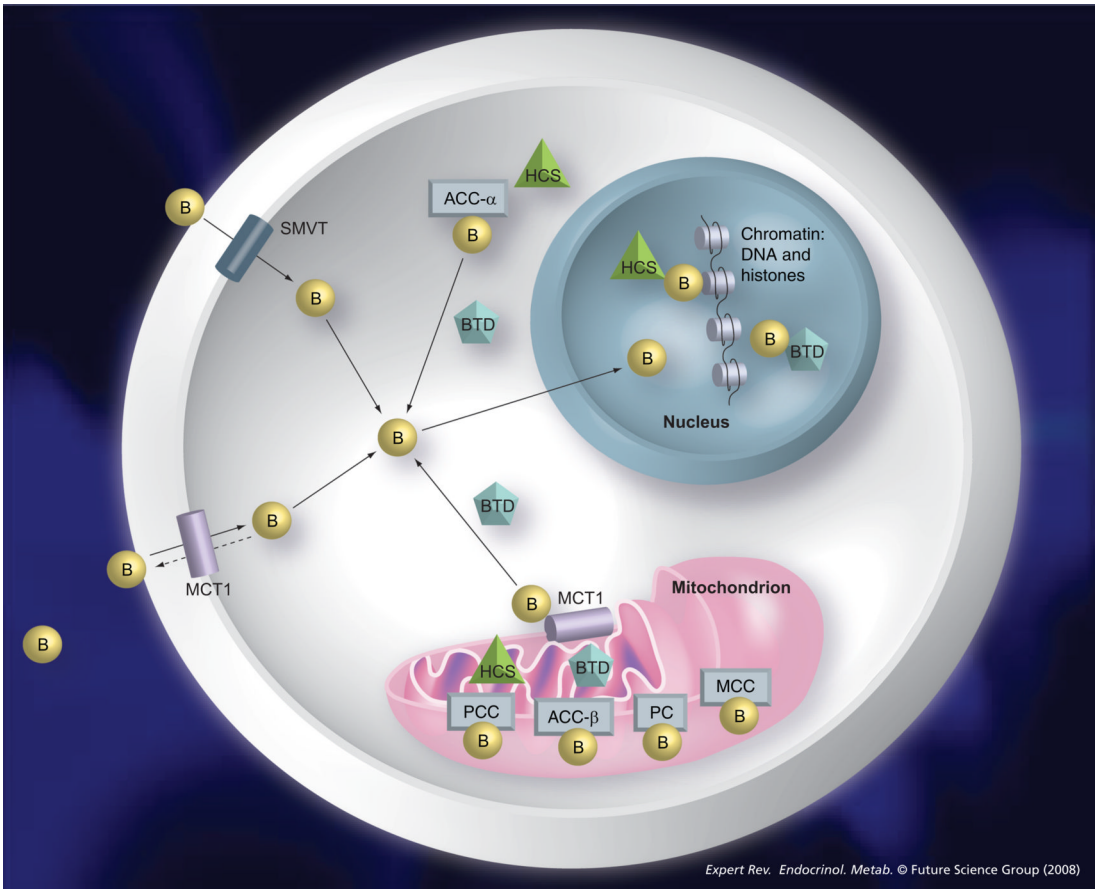

Figure 1. Biotin and its homeostasis

ACC: Acetyl-CoA carboxylase; B: Biotin; BTD: Biotinidase; HCS: Holocarboxylase synthetase; MCC: 3-methylcrotonyl-CoA carboxylase; MCT1: Monocarboxylate transporter 1; PC: Pyruvate carboxylase; PCC: Propionyl-CoA carboxylase; SMVT: Sodium-dependent multivitamin transporter.

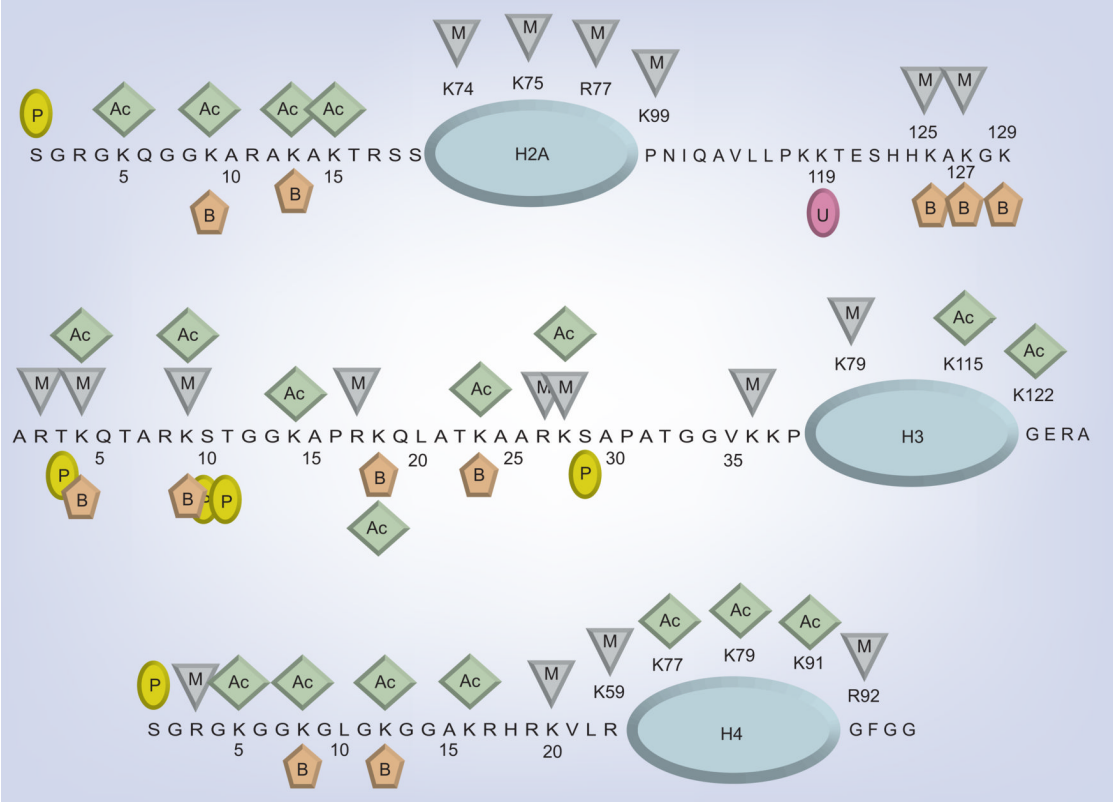

Figure 2. Modification sites in histones H2A, H3 and H4
Ac: Acetate; B: Biotin; M: Methyl; P: Phosphate; U: Ubiquitin.

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