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UPTAKE, LOCALIZATION, AND NONCARBOXYLASE ROLES OF BIOTIN*

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Key Words biotin, cell signaling, gene expression, histones, transport

■ **Abstract** Evidence is emerging that biotin participates in processes other than classical carboxylation reactions. Specifically, novel roles for biotin in cell signaling, gene expression, and chromatin structure have been identified in recent years. Human cells accumulate biotin by using both the sodium-dependent multivitamin transporter and monocarboxylate transporter 1. These transporters and other biotin-binding proteins partition biotin to compartments involved in biotin signaling: cytoplasm, mitochondria, and nuclei. The activity of cell signals such as biotinyl-AMP, Sp1 and Sp3, nuclear factor (NF)-κB, and receptor tyrosine kinases depends on biotin supply. Consistent with a role for biotin and its catabolites in modulating these cell signals, greater than 2000 biotin-dependent genes have been identified in various human tissues. Many biotin-dependent gene products play roles in signal transduction and localize to the cell nucleus, consistent with a role for biotin in cell signaling. Posttranscriptional events related to ribosomal activity and protein folding may further contribute to effects of biotin on gene expression. Finally, research has shown that biotinidase and holocarboxylase synthetase mediate covalent binding of biotin to histones (DNA-binding proteins), affecting chromatin structure; at least seven biotinylation sites have been identified in human histones. Biotinylation of histones appears to play a role in cell proliferation, gene silencing, and the cellular response to DNA repair. Roles for biotin in cell signaling and chromatin structure are consistent with the notion that biotin has a unique significance in cell biology.

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*__ABBREVIATIONS__: CNS, central nervous system; ER, endoplasmic reticulum; HCS, holocarboxylase synthetase; K_m, Michaelis-Menten constant; MCT, monocarboxylate transporter; PBMC, peripheral blood mononuclear cells; SMVT, sodium-dependent multivitamin transporter; UPR, unfolded protein response.

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INTRODUCTION

Soon after the discovery of biotin by Boas (12) and Kogl & Tonnis (75), biochemical functions of the vitamin were unveiled. It was demonstrated that biotin serves as a covalently bound coenzyme for the following carboxylases in eukaryotes: acetyl-CoA carboxylase, pyruvate carboxylase, propionyl-CoA carboxylase, and 3-methylcrotonyl-CoA carboxylase (74, 144). For acetyl-CoA carboxylase, a cytosolic (denoted acetyl-CoA carboxylase α) and a mitochondrial (denoted acetyl-CoA carboxylase β) form have been identified; the distinct functions of these isoforms in fatty acid metabolism have been reviewed (73). Acetyl-CoA carboxylase β may also play a role in biotin storage (120). Additional biotin-dependent carboxylases have been identified in prokaryotes (7, 49, 74, 144). Binding of biotin to carboxylases in eukaryotic cells is mediated by holocarboxylase synthetase (HCS); biotinyl-AMP occurs as an intermediate (44). Recycling of covalently bound biotin from breakdown products of carboxylases is mediated by biotinidase (142).

In the late 1960s and early 1970s, evidence began to emerge that biotin affects gene expression in mammals (45, 46). These pioneering studies can be considered the starting point for many of the exciting developments that the field of biotin research has witnessed in the recent past. Beginning with an improved understanding of cellular biotin uptake and localization, it became evident very quickly that biotin plays essential roles in cell signaling and chromatin structure. These recent advances in cellular uptake and localization, and the noncarboxylase roles of biotin, are reviewed in this chapter.

CELLULAR UPTAKE AND DISTRIBUTION

Mechanisms of biotin uptake into mammalian cells have been reviewed in detail in recent volumes in the *Annual Reviews* series (90, 116). The reader is referred to these reviews for a detailed account of biotin transporters. Here we provide a

brief update on biotin transporters located in the plasma membrane. Factors that determine the intracellular distribution of biotin are also discussed as they relate to newly discovered noncarboxylase roles of the vitamin.

Biotin Transporters in the Plasma Membrane

Early investigations of biotin transport in mammals provided evidence for the existence of a biotin carrier in plasma membranes (17, 18, 35). These studies suggested that uptake of biotin is a sodium-dependent process that requires metabolic energy. The Michaelis-Menten constant (K_m) of the biotin transporter in mouse fibroblasts 3T3-L1 and mouse jejunum is 22 and 3.7 μmol/L, respectively (35, 117). At high extracellular concentrations of biotin ([biotin] $\gg K_m$), passive diffusion of biotin into cells gains importance and exceeds carrier-mediated influx (18, 35). Both carrier-mediated uptake and passive diffusion account for the very efficient uptake of biotin observed in mammals. Oral doses of biotin that exceed the normal dietary intake by about 600 times are absorbed completely (150).

The biotin transporter in mammalian cells has broad substrate specificity and carries biotin, pantothenic acid, and lipoic acid (103) with similar affinity (105). Consequently, this transporter was named the sodium-dependent multivitamin transporter (SMVT) (105). The SMVT has been detected in numerous cell lines from various species (103–105, 116). Four variants of SMVT transcripts have been identified in rats (28). The role of SMVT in biotin transport was confirmed by cloning a cDNA coding for rat SMVT, and expressing functional transporter in human-derived HeLa cells (105). Likewise, rabbit intestinal SMVT was functionally expressed in human retinal pigment epithelium (104).

The intestinal biotin uptake is regulated by protein kinase C and Ca^{2+}/calmodulin-mediated pathways (115). Activation of protein kinase C inhibits biotin uptake, whereas inhibition of protein kinase C stimulates biotin uptake by Caco-2 cells. This effect of protein kinase C is mediated by alterations in the activity or abundance of biotin transporters, as opposed to alterations in transporter affinity for substrate. SMVT contains two putative protein kinase C phosphorylation sites (28, 104, 115), but it is unknown whether these sites are involved in the regulation of biotin uptake by protein kinase C.

The 5′-regulatory regions of *SMVT* genes in rats and humans have been cloned and characterized (29, 48). The rat and human *SMVT* genes contain three and two distinct promoters, respectively. Both promoter sequences in the human gene are TATA-less, CAAT-less, contain highly GC-rich sites, and have multiple putative regulatory *cis*-elements, e.g., AP-1, AP-2, C/EBP, SP1, NF1, and GATA (48). The minimal region required for basal activity of the human SMVT promoter is encoded by a sequence between −5846 and −5313 for promoter 1 and between −4417 and −4244 for promoter 2 relative to the translation initiation codon. The three promoters in the rat SMVT gene contain *cis*-elements similar to the elements observed in the human promoters, but the rat 5′-regulatory region also contains two TATA-like elements (29).

Notwithstanding the important role of SMVT in biotin uptake, the following lines of evidence suggest that transporters other than SMVT also mediate biotin

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uptake in some human tissues. First, the K_m for biotin uptake into human peripheral blood mononuclear cells (PBMC) is about 1000 times smaller than the K_m for biotin transport by SMVT (57, 149, 152). Second, both lipoic acid and pantothenic acid are substrates for SMVT but do not compete with biotin for uptake into PBMC (149, 152). Third, an inborn error in biotin transport does not affect transport of pantothenic acid in PBMC (87). Fourth, human lymphoid (Jurkat) cells respond to biotin deficiency with increased rates of biotin uptake without increasing the expression of SMVT (85).

Eventually evidence was provided that biotin uptake into human lymphoid cells is mediated by monocarboxylate transporter 1 (MCT1) in addition to SMVT (42). Notwithstanding the ubiquitous expression of MCT1 in human tissues (61), it remains to be demonstrated whether MCT1 plays a role in biotin uptake in tissues other than lymphoid cells (42). MCT1 belongs to the family of monocarboxylate transporters. Nine MCT-related sequences have so far been identified in mammals, each having a distinct tissue distribution (61). It is unknown if MCTs other than MCT1 play a role in biotin uptake.

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Biotin Homeostasis in the Central Nervous System

Disturbances in biotin homeostasis in the central nervous system (CNS) cause encephalopathies (41, 95). Factors leading to biotin imbalances in CNS include deficiencies of biotinidase, HCS (41), and perhaps biotin transporters (87, 95). Afflicted patients typically respond to the administration of large doses of biotin with maintaining normal neurological function (41, 95).

Moderate dietary biotin deficiency is typically not associated with neurological symptoms. This is consistent with the hypothesis that under conditions of moderate biotin deficiency the CNS maintains normal concentrations of biotin at the expense of other tissues. Indeed, research has shown that biotin deficiency causes a >90% decrease of biotinylated carboxylases in rat liver, whereas brain carboxylases remain unchanged (96). Apparently, biotin deficiency decreases expression of SMVT in rat liver while maintaining normal expression of SMVT in brain (96).

Biotin Uptake into Cellular Organelles

Biotin is distributed unequally across cellular compartments (100). If [^{14}C]biotin is administered intravenously to rats, the vast majority of biotin in liver localizes to mitochondria and cytoplasm, whereas only a small fraction localizes to microsomes (100). The relative enrichment of biotin in mitochondria and cytoplasm is consistent with the role of biotin as a coenzyme for carboxylases in these compartments. A quantitatively small but qualitatively important fraction of biotin localizes to the cell nucleus, i.e., about 0.7% of total biotin in human PBMC can be recovered from the nuclear fraction (128). The relative abundance of nuclear biotin increases to about 1% of total biotin in response to proliferation, consistent with a role for nuclear biotin-binding proteins (histones) in cell proliferation as described in the "Biological Functions of Histone Biotinylation" section.

What are the mechanisms driving the cellular partitioning of biotin? Theoretically, both transport by MCT1 (42) and binding to carboxylases (73, 74, 144) might mediate the sequestration of biotin in mitochondria. MCT1 is known to transport biotin (42) and has been detected in mitochondrial membranes (22, 61). After entry into mitochondria, biotin is trapped by covalent binding to acetyl-CoA carboxylase β, pyruvate carboxylase, propionyl-CoA carboxylase, and 3-methylcrotonyl-CoA carboxylase (74, 144). Studies of biotin turnover in human PBMC suggested that the half-life of biotin during the slow phase of elimination (half-life $= 21.9 \pm 13.6$ h) coincides with the breakdown of biotinylated carboxylases (151). Similar findings were made for biotin and holo-pyruvate carboxylase in the mouse preadipocyte cell line 3T3-L1 (54). Depletion and repletion studies of biotin-dependent carboxylases in rat liver are consistent with a role for mitochondrial acetyl-CoA carboxylase β in biotin storage (120).

Binding of biotin to proteins in cytoplasm and nucleus is likely to mediate the sequestration of biotin in these compartments. In cytoplasm, acetyl-CoA carboxylase α is the primary biotin-binding protein (147). In the cell nucleus, histones are the primary biotin-binding proteins (128).

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CELL SIGNALING

Gene Expression

Pioneering studies by Dakshinamurti and coworkers (43, 45, 46) provided evidence that biotin affects gene expression in addition to its classical role as a coenzyme for carboxylases. Specifically, these studies revealed that biotin deficiency in rats causes a 40% to 45% reduction of liver glucokinase activity, and that normal enzyme activity can be restored by biotin administration (45). Administration of biotin increases the amount of mRNA coding for glucokinase in rat liver (30, 126) and in cultured beta cells (14). These observations broke the ground for current investigations at the interface of biotin, cell signaling, gene expression, and human health.

DNA microarray studies have substantially expanded the number of genes known to be affected by biotin. Most of these studies were conducted using human PBMC and hepatocarcinoma (HepG2) cells. As of today, researchers have identified greater than 2000 human genes that depend on biotin for expression (109, 139, 140). Apparently, biotin-dependent genes are not randomly distributed in the human genome but are arranged in clusters. For example, supplementation of healthy adults with 8.8 μmol/d of biotin for 21 days was associated with increased and decreased expression of 139 and 131 genes, respectively, in PBMC compared with before biotin supplementation (140). The following clusters of biotin-responsive genes were identified in this study. First, if genes were clustered by biological function, biotin-dependent genes were overrepresented among genes associated with cell signaling. For example, at least 28% of biotin-responsive genes play roles in signal transduction, and 16% of products from biotin-responsive genes localize to the cell nucleus. Second, if genes were clustered by chromosomal location,

54% of biotin-responsive genes clustered on chromosomes 1, 2, 3, 11, 12, and 19, whereas no biotin-responsive genes were found on chromosomes 10, 16, 18, 21, and heterosomes. This suggests that position effects play a role in biotin-dependent gene expression.

In another study, human HepG2 cells were cultured in media containing deficient, physiological, and pharmacological concentrations of biotin or the catabolite bisnorbiotin (109). Approximately 1800 biotin-dependent genes were identified. A large number of biotin-dependent genes could be assigned to one of the following clusters based on molecular function: DNA-binding proteins, RNA-binding proteins, genes that play roles in translational activity, nucleotide-binding proteins, and proteins with transferase activity. Gene clusters associated with DNA-binding proteins, RNA-binding proteins, and nucleotide-binding proteins are consistent with a role of biotin in cell signaling and chromatin structure as described below.

The mechanisms that mediate the occurrence of biotin-dependent gene clusters are currently unknown. Both common regulatory elements in biotin-dependent genes and biotin-dependent remodeling of chromatin appear to play a role in this process. The following cell signals and transcription factors mediate effects of biotin on gene expression: (*a*) biotinyl-AMP and cGMP (125); (*b*) nuclear factor (NF)-κB (112); (*c*) Sp1 and Sp3 (59); and (*d*) receptor tyrosine kinases. These signaling pathways are reviewed in the following sections; biotin-dependent remodeling of chromatin is discussed further in the "Chromatin Structure" section.

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Biotinyl-AMP

Biotinyl-AMP is an intermediate in the synthesis of biotin-dependent holocarboxylases, catalyzed by HCS (147). In mammalian cells, HCS is localized in cytosol, mitochondria, and nucleus (27, 33, 94). Solorzano-Vargas et al. (125) proposed that biotinyl-AMP plays an essential role in regulating gene expression. According to this model, biotinyl-AMP activates soluble guanylate cyclase by a yet unknown mechanism; activation of guanylate cyclase increases the synthesis of cGMP (125). cGMP stimulates protein kinase G, leading to phosphorylation and activation of proteins that enhance the transcription of genes encoding HCS and some carboxylases. Transcriptional activation of these genes is impaired by both biotin deficiency and decreased activity of HCS; the latter can be observed in an inborn error of metabolism known as multiple carboxylase deficiency (131, 142). Consistent with the model described above, addition of biotin to biotin-deficient culture medium increased the activity of guanylate cyclase in both HeLa cells and fibroblasts (122). It remains to be determined whether activation of guanylate cyclase by biotinyl-AMP also plays a role in regulating the expression of genes other than holocarboxylase synthetase and carboxylases. Circumstantial evidence has shown that activation of guanylate cyclase by biotin supplementation is associated with increased activity of RNA polymerase II in HeLa cells and fibroblasts (122). These effects were observed at a concentration of 10 nmol/L biotin (122), which can be readily achieved in healthy adults by biotin supplementation (148).

Biotinyl-AMP-dependent cell signaling is also known from microorganisms. In *Escherichia coli* and other enteric bacteria, biotinyl-AMP [complexed with BirA (biotin-protein ligase), the microbial homolog of HCS] affects gene expression. The biotinyl-AMP/BirA complex binds to promoter regions in the biotin operon, a cluster of genes mediating biotin biosynthesis; binding of biotinyl-AMP/BirA represses the transcription of these genes (40). This feedback loop prevents excessive biosynthesis of biotin.

Nuclear Factor-κB

The transcription factor NF-κB regulates processes such as prevention of cell death, immune function, and embryonic development (81). Five members of the mammalian NF-κB/Rel family of transcription factors have been identified: c-Rel, NF-κB1 (p50/p105), NF-κB2 (p52/p100), RelA (p65), and RelB (4). Transcriptional activation of genes by NF-κB proceeds along the following mechanistic sequence. In unstimulated cells, heterodimers and homodimers of proteins from the NF-κB family reside in the cytoplasm (4). These inactive dimers are associated with the following monomers of inhibitors of NF-κB: IκBα or IκBβ (4). Binding to IκB retains NF-κB in the cytoplasm by masking the nuclear localization sequences (4). Stimulation of IκB kinases by bacteria, cytokines, mitogens, oxidative stress, growth factors, and hormones triggers phosphorylation of IκBs, which are then degraded in proteasome-dependent pathways (81). The liberated NF-κB dimers translocate to the cell nucleus, where they bind to response elements in regulatory regions of genes, triggering gene expression.

Research has shown that biotin affects cell signaling by NF-κB (112). In these studies, human-derived lymphoma (Jurkat) cells were cultured in biotin-deficient and biotin-supplemented media for five weeks; cells were stimulated with phytohemagglutinin and phorbol-12-myristate-13-acetate to induce nuclear translocation of NF-κB. The following observations are consistent with the hypothesis that biotin supply affects NF-κB signaling: (*a*) the nuclear abundance of p50 and p65 is greater in biotin-deficient cells compared with biotin-supplemented cells; (*b*) the DNA-binding activity of NF-κB is greater in biotin-deficient cells compared with biotin-supplemented cells; (*c*) the transcriptional activity of NF-κB-dependent reporter genes is greater in biotin-deficient cells compared with biotin-supplemented cells; and (*d*) the activity of IκBα kinases is greater in biotin-deficient cells compared with biotin-supplemented cells, consistent with increased rates of IκBα degradation and nuclear translocation of NF-κB.

Many cancer cells activate NF-κB in response to treatment with antineoplastic drugs (13, 47, 138), mediating expression of antiapoptotic genes such as *Bfl-1/A1* (6, 52, 66, 81). The products of these genes enhance survival of cancer cells (70, 137, 138), causing resistance to chemotherapy. Research has shown that biotin deficiency enhances the nuclear translocation of NF-κB in Jurkat cells treated with antineoplastic agents such as taxol, doxorubicin, and vinblastine (60). This is associated with increased expression of Bfl-1/A1 and a decreased rate of death in cells treated with doxorubicin and vinblastine. It is uncertain whether

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biotin status of cancer patients affects the resistance to chemotherapy in vivo. Notwithstanding this uncertainty, effects of biotin on NF-κB activity and cell survival are of potential relevance for health care professionals, given the high prevalence of nutrient deficiencies in cancer patients and during chemotherapy (71, 123, 124).

Sp1 and Sp3

Sp1 and Sp3 belong to the Sp/Krüppel-like factor (KLF) family of transcription factors, which contains at least 20 distinct proteins in mammals (11). Some members of this family are widespread or ubiquitously expressed, whereas other members are highly restricted in their tissue distribution (11). Sp/KLF transcription factors have overlapping DNA-binding specificities and bind to GC-rich sequences (e.g., GC boxes, CACCC boxes) located in regulatory regions of numerous genes; these sequences are collectively referred to as Sp1 sites. Competition among family members for binding to regulatory sequences in DNA plays an important role in the regulation of gene expression (11). Sp/KLF transcription factors differ in their transcriptional activity, with some being activating and some being repressive, establishing a very complex network of regulation. For example, Sp3 may repress Sp1-dependent activation of genes encoding dihydrofolate reductase and α1(II) procollagen by competing with Sp1 for binding to Sp1 sites (10, 55).

The nuclear abundance of Sp1 and Sp3 depends on biotin status in Jurkat cells; the DNA-binding activity of Sp1 and Sp3 is up to 149% greater in biotin-supplemented cells compared with biotin-deficient cells (59). The increased DNA-binding activity in biotin-supplemented cells is mediated by increased expression of genes coding for Sp1 and Sp3. In contrast, posttranslational phosphorylation of Sp1 and Sp3 [a modification known to affect DNA-binding activity (2, 80, 93, 114)] does not depend on biotin (59). Preliminary evidence suggests that Sp1 and Sp3 might be directly modified by covalent binding of biotin (J. Zempleni, unpublished observation). The increased nuclear abundance of Sp1 and Sp3 in biotin-supplemented cells is associated with increased transcriptional activity of Sp1/Sp3-dependent reporter-gene constructs compared with biotin-deficient controls (59).

Effects of biotin on the nuclear abundance of Sp1 and Sp3 are physiologically important. First, the increased nuclear abundance of Sp1 and Sp3 in biotin-supplemented lymphoid cells is associated with increased expression of the *cytochrome P450 1B1* gene (108). The 5′-flanking region of the human *cytochrome P450 1B1* gene contains 11 Sp1 sites (132, 135, 141). Cytochrome P450 1B1 hydroxylates xenobiotics and estrogens ("metabolic activation"), creating electrophilic mutagens that may cause single-stranded breaks in DNA and 8-hydroxylation of guanine bases in DNA (64, 82). Indeed, biotin supplementation is associated with increased frequency of DNA strand breaks in lymphoid cells (108).

Second, biotin supplementation is associated with decreased transcription of the *sarco/endoplasmic reticulum ATPase3* (*SERCA3*) gene (58), the expression of

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which is controlled by 25 Sp1 sites in its 5′-flanking region (50). Given that Sp3 may act as transcriptional repressor, it has been proposed that effects of biotin on SERCA3 expression are mediated by the increased nuclear abundance of Sp3 in biotin-supplemented cells (58). Decreased expression of SERCA3 reduces the sequestration of calcium in the endoplasmic reticulum (ER) (83). This impairs activities of calcium-dependent proteins such as calnexin (8, 63), BiP (84), and protein disulfide isomerase (84), which play essential roles in the folding of secretory proteins. Accumulation of unfolded proteins in the ER triggers a process named the unfolded protein response (UPR) (121). Hallmarks of UPR include a low global translational activity, a specific increase in the expression of chaperones and other stress-related proteins, a decreased rate of cell proliferation, and an increase in apoptotic activity (20, 25, 97, 106, 121, 146). The following lines of evidence suggest that low expression of SERCA3 in biotin-supplemented cells impairs protein folding in the ER, triggering UPR (58): (*a*) sequestration of calcium in the ER decreased by 30% in response to biotin supplementation; (*b*) secretion of interleukin-2 into the extracellular space decreased by 75% in response to biotin supplementation; and (*c*) the abundance of stress-related proteins such as UBE1, GADD153, XBP1, and phosphorylated eIF2α increased in response to biotin supplementation.

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Receptor Tyrosine Kinase Signaling

Receptor tyrosine kinases span the membranes of mammalian cells (65). Various ligands have affinity for the ligand-binding site located in the extracellular domain of receptor tyrosine kinases; ligands include platelet-derived growth factor, insulin, thrombin, and various other compounds. Binding of ligands causes dimerization of receptors and activation of the tyrosine kinase domain located in the cytoplasmic region; this is associated with autophosphorylation of the C-terminus of the receptor. Phosphorylated receptor has affinity for GRB2 (and perhaps its homolog SAM68) and SOS. Binding of the G protein SOS to the phosphorylated receptor tyrosine kinase triggers a substitution of GTP for GDP in the serine/threonine kinase Ras, leading to its catalytic activation. Phosphorylated Ras mediates phosphorylation and, hence, activation of the serine/threonine kinase RAF1. RAF1 phosphorylates MAP kinase kinases (MAPKK or MEK). Phosphorylated MEK catalyze phosphorylation and, hence, activation of mitogen-activated protein kinases (MAPK) such as ERK1 and ERK2. Phosphorylated ERK mediate phosphorylation of the transcription factors Fos and Jun, which bind to AP1 sites in regulatory regions of genes, causing transcriptional activation.

Research has shown that biotin deficiency activates signaling by receptor tyrosine kinases. In these studies, human hepatocarcinoma (HepG2) cells were cultured in media containing deficient, physiological, or pharmacological concentrations of biotin for 10 days (107). Proteins in cell extracts were quantified using high-throughput immunoblots. Biotin deficiency was associated with increased abundance of GRB2, SAM68, and RAF1; the abundance of the Ras-interacting protein

AF6 decreased to nondetectable levels in response to biotin deficiency, enhancing the activity of Ras. Activation of receptor tyrosine kinase pathways was associated with nuclear translocation of AP1-binding proteins Jun and Fos, and transcriptional activation of AP1-dependent reporter genes in biotin-deficient HepG2 cells. The physiological significance of this finding is uncertain. AP1 sites render genes responsive to stimulation with phorbol esters (77); the 5′-flanking region of the human *SMVT* gene also contains AP1 sites (48). Theoretically, activation of receptor tyrosine kinase signaling in biotin-deficient cells may contribute to increasing SMVT-mediated biotin uptake.

Biotin Catabolites

McCormick and coworkers have described the two major pathways of biotin catabolism in a series of seminal papers (89). In the first pathway, biotin is catabolized by β-oxidation of the valeric acid side chain, generating compounds such as bisnorbiotin and tetranorbiotin. In the second pathway, the sulfur in the thiophane portion of the biotin molecule is oxidized, generating compounds such as biotin-*d*, l-sulfoxides and biotin sulfone. Combinations of both β-oxidation and sulfur oxidation also occur to generate compounds such as tetranorbiotin-l-sulfoxide. Biotin catabolites are quantitatively important in mammalian body fluids and cells; the total concentration of biotin catabolites approximately equals the concentration of intact biotin (91, 92).

Evidence emerged that biotin catabolites may play roles in cell signaling. In Jurkat cells, biotin deficiency is associated with decreased expression of the genes encoding interleukin-2 and interleukin-2 receptor gamma (110). Supplementation of biotin-deficient culture medium with the synthetic biotin derivatives diaminobiotin and desthiobiotin restored expression of interleukin-2 and interleukin-2 receptor gamma to control levels (110). Supplementation of culture media with diaminobiotin and desthiobiotin did not affect the abundance of holocarboxylases and activities of propionyl-CoA carboxylase. Hence, effects of biotin analogs on gene expression are not mediated by carboxylase-dependent pathways. Modulation of gene expression by biotin analogs extends to naturally occurring biotin catabolites. For example, supplementation of culture medium with bisnorbiotin altered the expression of 618 genes in HepG2 cells (109).

The mechanisms by which biotin catabolites affect gene expression are uncertain. Note that HCS cannot convert biotin analogs such as desthiobiotin to AMP esters (134); in addition, biotin analogs such as biocytin (biotin-ε-lysine), desthiobiotin, diaminobiotin, and iminobiotin do not inhibit the enzymatic conversion of biotin to biotinyl-AMP, suggesting that these analogs do not compete with biotin for binding to HCS (134). Thus, effects of biotin catabolites on gene expression cannot be explained by the biotinyl-AMP model. Future studies are likely to reveal the mechanism by which biotin catabolites modify gene expression, including the possibility that catabolites may have a biotin-sparing effect in human cells. Notwithstanding the uncertainties described above, effects of biotin catabolites on gene expression are of important consideration for nutritionists. Given that biotin

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catabolites account for at least 50% of total biotinyl compounds in mammalian tissues (and, hence, foodstuffs) (91), previous studies may have underestimated the true food content and dietary intake of bioactive biotinyl compounds.

Posttranscriptional Events

Effects of biotin on gene expression and cell signaling are not limited to the transcriptional level but also include posttranscriptional events. The earliest studies pointing to a role for biotin in posttranscriptional events date back to the late 1980s (38). These studies provided evidence that the expression of the asialoglycoprotein receptor is reduced in biotin-deficient HepG2 cells, whereas total cellular protein content and mRNA coding for the asialoglycoprotein receptor are comparable to those of control cells; addition of biotin or biocytin to culture media restored receptor expression (38). Analogous studies of propionyl-CoA carboxylase in rat hepatocytes suggested that biotin might also affect the expression of this carboxylase at a posttranscriptional step (111). The mechanisms leading to these effects of biotin are largely unknown. Theoretically, the formation of translation initiation complexes may depend on biotin. Consistent with this notion, the expression of ribosomal subunits LP2, L27a, L38, S11, and S19 and translation initiation factor eIF5A increases in response to biotin deficiency in HepG2 cells (109). In contrast, expression of the ribosomal subunits L37a, S5, and S21 increases in response to biotin supplementation.

HISTONES

Chromatin Structure

Chromatin in the mammalian cell nucleus is composed primarily of DNA and DNA-binding proteins, i.e., histones and nonhistone proteins. Histones play a predominant role in the folding of DNA into chromatin (143). Five major classes of histones have been identified in mammals: H1, H2A, H2B, H3, and H4. Histones are small proteins (11 to 22 kDa) consisting of a globular domain and a more flexible amino terminus (histone "tail"). Lysine and arginine residues combined account for $>20\%$ of all amino acid residues in histones, leading to a positive net charge of these proteins at physiological pH (143).

DNA and histones form repetitive nucleoprotein units, the nucleosomes (143). Each nucleosome ("nucleosomal core particle") consists of 146 base pairs of DNA wrapped around an octamer of core histones (one H3-H3-H4-H4 tetramer and two H2A-H2B dimers). The binding of DNA to histones is of electrostatic nature, and is mediated by the association of negatively charged phosphate groups of DNA with positively charged ε-amino groups (lysine moieties) and guanidino groups (arginine moieties) of histones. The DNA located between nucleosomal core particles is associated with histone H1.

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

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for gene regulation (21, 56, 69, 88, 101, 133), mitotic and meiotic chromosome condensation (34), and DNA repair (1, 9, 16, 51, 72, 145). Histone tails are modified by covalent acetylation (3, 62, 79), methylation (143), phosphorylation (143), ubiquitination (143), poly (ADP-ribosylation) (15, 16, 26), and biotinylation (see below) of ϵ-amino groups (lysine), guanidino groups (arginine), carboxyl groups (glutamate), and hydroxyl groups (serine). Multiple signaling pathways converge on histones to mediate covalent modifications of specific amino acid residues (31, 78). Site-specific modifications of histones have distinct functions; for example, dimethylation of lysine-4 in histone H3 is associated with transcriptional activation of surrounding DNA (53, 69). Modifications of histone tails ("histone code") considerably extend the information potential of the DNA code and gene regulation (69, 129, 136). Modifications of histone tails may affect binding of chromatin-associated proteins, triggering cascades of downstream histone modifications. For example, methylation of arginine-3 in histone H4 recruits the histone acetyl transferase Esa1 to yeast chromatin, leading to acetylation of lysine-5 in histone H4 (69). Histone modifications can influence each other in synergistic or antagonistic ways, mediating gene regulation. For example, phosphorylation of serine-10 inhibits methylation of lysine-9 in histone H3, but it is coupled with acetylation of lysine-9 and lysine-14 during mitogenic stimulation in mammalian cells (69). Covalent modifications of histones can be reversed by a large variety of enzymatic processes (69).

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Enzymatic Biotinylation and Debiotinylation of Histones

Histones are modified by covalent attachment of the vitamin biotin. Hymes et al. (67, 68, 113) have proposed a reaction mechanism by which cleavage of biocytin (biotin-ε-lysine) by biotinidase leads to the formation of a biotinyl-thioester intermediate (cysteine-bound biotin) at or near the active site of biotinidase. In a next step, the biotinyl moiety is transferred from the thioester to the ε-amino group of lysine in histones. Biocytin is generated in the breakdown of biotin-dependent carboxylases, which contain biotin linked to the ε-amino group of a lysine moiety (102, 142).

Biotinidase belongs to the nitrilase superfamily of enzymes, which consists of 12 families of amidases, N-acyltransferases, and nitrilases (19). Some members of the nitrilase superfamily (vanins-1, -2, and -3) share significant sequence similarities with biotinidase (86); it is unknown whether vanins use histones as acceptor molecules in transferase reactions. Biotinidase is ubiquitous in mammalian cells and 26% of the cellular biotinidase activity is located in the nuclear fraction (102). Human biotinidase has been characterized at the gene level (36, 37). 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 HNF-5 site, but has no TATA element (37). The 62-amino acid region that harbors the active site of biotinidase is highly conserved among various mammals and *Drosophila* (130).

Subsequent to the elucidation of the biotinidase-mediated mechanism of histone biotinylation in vitro (67, 68), biotinylated histones H1, H2A, H2B, H3, and H4 were detected in human PBMC in vivo (128). Biotinylated histones were also detected in human lymphoma cells (85), small cell lung cancer cells (119), choriocarcinoma cells (39), and chicken erythrocytes (98). These studies also suggested that biotinidase may not be the only enzyme mediating histone biotinylation. For example, evidence showed that biotinylation of histones increases in response to cell proliferation, whereas biotinidase activity was similar in nuclei from proliferating cells and quiescent controls (128). Finally, Gravel and coworkers (94) identified HCS as another enzyme that may catalyze biotinylation of histones.

Mechanisms mediating debiotinylation of histones are largely unknown. Recent studies suggested that biotinidase might catalyze both biotinylation and debiotinylation of histones (5). Variables such as the microenvironment in chromatin and posttranslational modifications and alternate splicing of biotinidase might determine whether biotinidase 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 (67) and the debiotinylating activity of biotinidase (5). Second, proteins may interact with biotinidase at the chromatin level, favoring either biotinylation or debiotinylation of histones. Third, three alternatively spliced variants of biotinidase have been identified (127). Theoretically, these variants may have unique functions in histone metabolism. Fourth, some variants of biotinidase are modified posttranslationally by glycosylation (36, 127), potentially affecting enzymatic activity.

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Identification of Biotinylation Sites

Biotinylation sites in human histones were identified by using synthetic peptides (23, 24). Briefly, this approach is based on the following analytical sequence: (*a*) short peptides (<20 amino acids in length) are synthesized chemically; the amino acid sequences in these peptides are based on the sequence in a given region of a given histone; (*b*) peptides are incubated with biotinidase or HCS to conduct enzymatic biotinylation; (*c*) peptides are resolved by electrophoresis; and (*d*) biotin in peptides is probed using streptavidin peroxidase. Amino acid substitutions (e.g., lysine-to-alanine substitutions) and modifications (e.g., acetylation of lysines) in synthetic peptides can be used to corroborate identification of biotinylation sites and to investigate the cross-talk between biotinylation and other known modifications of histones, respectively (24). Using this approach, the following biotinylation sites have been identified in human histones: K9 and K13 in histone H2A (J. Zempleni, unpublished observation), K4, K9, and K18 in histone H3 (118), and K8 and K12 in histone H4 (24). Acetylation and phosphorylation

of lysine and serine residues, respectively, decrease biotinylation of adjacent lysine residues (24, 118). In contrast, dimethylation of arginine residues enhances biotinylation of adjacent lysine residues (118). This is consistent with studies suggesting that histones in livers from biotin-deficient rats showed unusual patterns of phosphorylation, methylation, and acetylation compared with biotin-sufficient controls (99).

Biological Functions of Histone Biotinylation

Biotinylation of histones is a relatively new field of research; evidence of biological roles for biotinylation of histones is scarce. However, biotinylation of histones appears to participate in the following biological processes.

First, evidence showed that biotinylation of histones increases in response to cell proliferation in human PBMC (128). Biotinylation of histones increases early in the cell cycle (G1 phase) and remains increased during later phases (S, G2, and M phase) compared with quiescent controls; the increase is greater than fourfold. Fibroblasts from patients with HCS deficiency are severely deficient in histone biotinylation (94). It remains to be determined whether this is associated with decreased proliferation rates. Note that these studies were conducted before specific biotinylation sites in histones were identified and before biotinylation site-specific antibodies became available. Thus, these studies did not allow pinpointing changes in specific biotinylation sites; rather, the global biotinylation of histones was quantified by using streptavidin or radiolabeled biotin.

Second, studies in chicken erythrocytes have provided circumstantial evidence that biotinylated histones are enriched in transcriptionally silent chromatin (98).

Third, biotinylation of histones might play a role in the cellular response to DNA damage (76, 98). If formation of thymine dimers is caused by exposure of lymphoid cells to UV light, the global biotinylation of histones increases (98). If double-stranded DNA breaks are caused by exposure of lymphoid and choriocarcinoma cells to etoposide, biotinylation of K12 in histone H4 shows a rapid and transient decrease (76). This is consistent with a role for histone biotinylation in signaling DNA damage. These studies suggest that distinct kinds of DNA damage cause unique changes in histone biotinylation. Currently, it is unknown whether biotinylation of histones is a mechanism leading to DNA repair or apoptosis.

Biotin Supply

Effects of biotin supply on biotinylation of histones have been investigated in various human-derived cell lines (39, 85, 119). In these studies, cell lines were cultured in media containing deficient, physiological, and pharmacological concentrations of biotin for several weeks. Biotin concentrations in culture media had only a moderate impact on biotinylation of histones; in contrast, biotinylation of carboxylases correlated strongly with biotin concentrations in culture media (39, 85, 119). The reader should note that even small changes in biotinylation of

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histones might be physiologically meaningful, given that these changes might affect other modifications of histones such as acetylation and methylation.

CONCLUSIONS AND OUTLOOK

In recent years, the groundwork has been laid to characterize roles for biotin in gene expression, cell signaling, and chromatin structure. Numerous clusters of biotin-dependent genes and signaling pathways have been identified. Biotin-dependent signaling pathways regulate the expression of genes that have important biological functions, e.g., in apoptosis and cell survival. Importantly, biotin-dependent cell signals converge at the level of chromatin: At least seven lysine residues in human histones are targets for biotinylation by biotinidase and HCS. Biotinylation of histones appears to be associated with cell proliferation, gene silencing, and the cellular response to DNA damage. Likely, more biotinylation sites in histones await identification. We anticipate that roles of biotin in cell signaling and chromatin structure will lead to the discovery of numerous novel roles for biotin in cell biology and human health, e.g., prevention of tumor initiation. Finally, one can expect to discover new biotinylated proteins in eukaryotic cells. Consistent with this assumption, we have identified novel biotinylation motifs in human proteins, including important signaling molecules (J. Zempleni, unpublished observation). Identification of new biotinylated proteins is likely to add substantially to the importance of biotin in cell biology.

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