REVIEW ARTICLE

Transcriptional regulation of genes for ornithine cycle enzymes

Masaki TAKIGUCHI and Masataka MORI

Department of Molecular Genetics, Kumamoto University School of Medicine, Kuhonji 4-24-1, Kumamoto 862, Japan

INTRODUCTION

The ornithine cycle [1], also called the urea cycle, is an enzyme system that converts ammonia into urea (for recent reviews, see [2–4]) (Figure 1). Ammonia, which is produced mainly by amino acid metabolism, is toxic to higher animals, and must be excreted or detoxified. Fish and amphibian larvae such as tadpoles excrete ammonia from the gills directly into the surrounding water. Mammalian fetuses transfer ammonia to their mothers. Amphibian metamorphosis and mammalian birth, which lead to independent life on land, are accompanied by induction of the ornithine cycle in the liver. This enables the animals to convert ammonia into urea, which is less toxic and can be stored prior to excretion. Urea synthesized in the liver is transported to the kidney, and then excreted. On the other hand, in birds and terrestrial reptiles, ammonia is converted into uric acid, which is practically water-insoluble and can be stored in a solid form in a shelled egg.

The ornithine cycle consists of five enzymes (Figure 1); the first enzyme, carbamoyl-phosphate synthase I (CPS; EC 6.3.4.16), and the second enzyme, ornithine transcarbamylase (OTC; EC 2.1.3.3), are located in the mitochondrial matrix, and the remaining three enzymes, argininosuccinate synthase (AS; EC 6.3.4.5), argininosuccinate lyase (AL; EC 4.3.2.1) and arginase (EC 3.5.3.1), are present in the cytosol. CPS and OTC have provided useful systems for the study of intracellular traffic and the processing of nuclear-gene-encoded mitochondrial proteins [5–8]. Inborn errors in any of the five enzymes can result in insufficient ammonia detoxification, leading to hyperammonaemia (reviewed in [4]). Besides these five enzymes, *N*-acetylglutamate synthase (EC 2.3.1.1), which catalyses the formation of *N*-acetylglutamate, an obligatory allosteric activator of CPS, participates in the regulation of urea biosynthesis. This enzyme has been purified and characterized from the rat [9,10] and human [11] liver. A deficiency of this enzyme also results in hyperammonaemia [12].

The ornithine cycle enzymes, except for arginase, that are present in non-hepatic tissues (see below) are mainly involved in arginine biosynthesis (as recent reviews, see introductions of [13,14]). In fact, the ornithine cycle is thought to have evolved from the arginine-synthetic pathway (reviewed in [15]). This notion is substantiated by sequence identities between the ornithine cycle enzymes of mammals and the corresponding arginine-biosynthetic enzymes of micro-organisms such as *Escherichia coli* and yeast (reviewed in [16]).

TISSUE-SELECTIVE EXPRESSION

All five ornithine cycle enzymes are abundant in liver parenchymal cells, i.e. hepatocytes, where the enzymes constitute the complete cycle. Localization of the enzymes in the liver lobule

has been most precisely studied with rat CPS, which was shown to be present exclusively in the periportal compartment and not in the pericentral compartment [17]. This zonation becomes evident by 3 days after birth for CPS mRNA [18] and by 6 days for CPS protein [19]. Dietary and hormonal changes that induce CPS (see below) cause a reversal of the distribution of CPS mRNA along the porto-central axis in the lobule [20].

Besides the liver, CPS and OTC are highly expressed in mucosal epithelial cells of the small intestine [21,22]. AS and AL are also expressed in proximal tubules of the kidney [13,23,24] and in the testis [25], as well as at lower levels in many other tissues [25–27]. These non-hepatic enzymes contribute to the biosynthesis of arginine, as described above. Regulation of the genes for the ornithine cycle enzymes in the small intestine [28–32] and kidney [24,33] differs from that in the liver in developmental, nutritional and hormonal aspects, as reviewed in [3].

Studies on the transcriptional regulation of many genes that are expressed specifically in the liver led to the identification of a number of liver-selective transcription factors, some of which interact with regulatory regions of the genes for the ornithine cycle enzymes. At present, liver-selective transcription factors are categorized into five groups: (i) members of the CCAAT/enhancer binding protein (C/EBP) family, i.e. C/EBP α [34] and C/EBP β [35], also known as NF-IL6 [36], IL6-DBP [37], LAP [38], AGP/EBP [39] and CRP2 [40], which contain the basic region/leucine zipper; (ii) the albumin D-element binding protein (DBP) [41], a member of another basic region/leucine zipper protein family; (iii) hepatocyte nuclear factor-1 (HNF-1) [42,43], which has an extra-large homeodomain; (iv) HNF-3 family members [44,45], which contain a DNA-binding domain highly homologous to that of the *fork head* protein in *Drosophila*; and (v) HNF-4 [46], a member of the steroid receptor superfamily.

REGULATION IN THE CONTEXT OF NITRIC OXIDE SYNTHESIS

Arginine, the substrate of arginase, the final enzyme in the cycle, can also be converted into nitric oxide (NO) by nitric oxide synthase (NOS) (Figure 1). NO exhibits various biological functions such as neurotransmission, regulation of blood pressure, and macrophage bactericidal and tumoricidal activities (reviewed in [47–49]). In addition to NO, NOS yields citrulline, which can then be utilized to regenerate arginine through serial catalysis by AS and AL. Therefore NOS, AS and AL constitute a cycle that can be regarded as bypassing the ornithine cycle; this has been called the citrulline–NO cycle [50], or the arginine–citrulline cycle [51]. Three NOS isoenzymes have been cloned: neuronal or brain constitutive NOS (nNOS or bNOS), cloned from rat [52], mouse [53] and human [54] brain; vascular endothelial constitutive NOS (eNOS), cloned from bovine [55,56]

Figure 1 (a) Ammonia detoxification mechanisms and (b) the ornithine cycle (urea cycle)

(a) Differences in ammonia detoxification with phylogeny and ontogeny of vertebrates. Toxic ammonia is excreted unchanged (this phenomenon is called ammonotelism) or converted into urea (ureotelism) or uric acid (uricotelism) prior to excretion. Representative animals of each form are shown. At the metamorphosis of amphibians and the birth of mammals, the ornithine cycle is induced in the liver, and the animals change from the ammonotelic to the ureotelic form. (b) The ornithine cycle, its enzymes, and its relationship with the citrulline-NO cycle. The ornithine cycle converts toxic ammonia into relatively non-toxic urea, through five enzymic steps shown by black and red solid arrows. NOS catalyses the reaction shown by broken red arrows. Reactions shown by red solid and broken arrows constitute the citrulline-NO cycle, which can be regarded as a bypass of the ornithine cycle. Enzymes: 1, CPS; 2, OTC; 3, AS; 4, AL; 5, arginase.

and human [57] endothelial cells; and inducible NOS (iNOS), cloned from a number of sources, e.g. a mouse macrophage cell line [58–60], rat [61,62] and human [63] liver, human chondrocytes [64], rat vascular smooth muscle [65], a human colorectal adenocarcinoma cell line [66] and a human glioblastoma cell line [67]. The iNOS gene is activated in response to stimuli such as lipopolysaccharide and interferon- γ (reviewed in [47–49]). In macrophage [50] and vascular smooth muscle [51] cell lines, these stimulants also induce AS mRNA and enzyme activity, in a co-ordinated manner with those of iNOS. This phenomenon is consistent with the notion of the presence of the citrulline-NO cycle. The cells in which the citrulline-NO cycle functions *in vivo*, and the extent to which the genes for NOS and AS are similarly regulated, are the subjects of ongoing investigations.

DEVELOPMENTAL, NUTRITIONAL AND PATHOLOGICAL REGULATION IN THE LIVER

In the liver, the genes for the five ornithine cycle enzymes are usually regulated in a co-ordinated manner. In frogs, thyroid hormones that are crucial for metamorphosis also appear to trigger induction of these enzymes [68]. In tadpoles of *Rana catesbeiana* and *Xenopus laevis*, precocious treatment with thyroid hormones causes accumulation of mRNAs for all five enzymes: CPS [69–72], OTC [71,72], AS [69], AL [73] and arginase [72–74]. The accumulation of mRNAs is preceded by time lags of between one and several days [69,71,72,74]. In this latent period, the autoinduction of mRNAs for thyroid hormone receptors occurs [71,74]; this is a characteristic phenomenon that is generally observed during metamorphosis [75,76].

In mammals, the earliest expression of ornithine cycle enzymes during development was reported for arginase, which can be detected on embryonic day 10.75 of the rat, soon after hepatocytes differentiate from the embryonic foregut [77]. mRNAs for all five enzymes are detectable by embryonic day 13 of the mouse [78]. mRNA levels for CPS, AS and arginase increase sharply on day 17, and those for AL and OTC increase on day 19 (the day of birth) and on day 21 respectively [78]. Similar profiles were observed for the mRNAs of rat CPS [79,80], OTC [81], AS [79] and AL [82].

Postnatally, the enzyme genes are regulated nutritionally. A high protein intake [83,84] and starvation [85], which augment ammonia production, lead to increases in the activities of all ornithine cycle enzymes in rat [83,85] and monkey [84] liver. Increases in the enzyme activities generally correlate with increases in mRNA levels [21,86,87], except for decreases in translational mRNA activities [86] despite increases in mRNA concentrations [87] for CPS and OTC in starved rats. Changes in the rates of degradation of the enzyme proteins also seem to contribute to changes in enzyme levels [88–90].

Two lines of mutant mice in which some metabolic defect results in reduced expression of the ornithine cycle enzymes have been characterized. One line is the albino c^{14Cos} mouse (reviewed in [91–93]), which contains a lethal mutation and dies shortly after birth, presumably as a result of hypoglycaemia. The affected locus responsible for this mortality proved to be the gene for fumarylacetoacetate hydrolase, an enzyme involved in tyrosine metabolism [94–97]. In the livers of these mice, the expression of genes for the ornithine cycle enzymes is decreased [96,98,99], as is the case for the genes of other liver-selective proteins (reviewed in [93]), including transcription factors [99–102]. Another mutant line is the juvenile visceral steatosis (*jvs*) mouse [103], which suffers from severe lipid accumulation in the liver and dies within 5–6 weeks after birth. The affected genetic locus remains to be identified, but the primary defect was suggested to be reduced reabsorption in the kidney of carnitine, a compound involved in the transport of fatty acids across the mitochondrial inner membrane [104]. In the livers of *jvs* mice, the activities of ornithine cycle enzymes [103], their mRNA levels and the transcriptional activities of their genes [105] are all decreased. Administration of carnitine to the mutant mice relieves the reduced expression of these genes [106]. On the other hand, a number of transcription factors, including liver-selective ones, appear to be in an activated state in these mice [107]. The mechanisms that underlie the reduced expression of the genes for the ornithine cycle enzymes in these mutant mice remain to be elucidated.

HORMONAL REGULATION

The developmental and nutritional changes described above seem to be mediated, at least in part, by hormones. Glucocorticoids and glucagon (or analogues of cyclic AMP, the second messenger of glucagon) elevate the activities [108–113] and the mRNA levels [87,114,115] of the ornithine cycle enzymes, except for OTC, in the rat liver, primary cultured hepatocytes and hepatoma cell lines. Increases in mRNA levels or protein synthesis rates were also noted for CPS [31,116–120], AL [82,121,122] and arginase [123]. For CPS [117–119] and AL [121], it was reported that insulin represses these inductions.

Characteristically, inductions of ornithine cycle enzyme genes by glucocorticoids are not directly effected by the glucocorticoid-receptor complex; rather, they are mediated by some protein factor(s) synthesized *de novo* in response to the hormone [114] (see below). On the other hand, cyclic AMP elevates mRNA

levels without requiring ongoing protein synthesis [114]. A genetic locus designated tissue-specific extinguisher 1 (*Tse-1*), which is responsible for the repression of a number of liver-selective genes (including CPS and AS genes) in hepatoma-cell-fibroblast hybrids [99,124,125], was shown to encode the regulatory subunit (RI α) of protein kinase A [126,127]. This is in accordance with the notion that activation of CPS and AS genes by glucagon and cyclic AMP requires protein kinase A activity.

In this review, we focus on recent studies into the transcriptional regulation of the ornithine cycle enzyme genes, as elucidated mainly through analyses of regulatory regions such as promoters and enhancers (Figure 2). Regulation of the cycle at the level of enzyme protein and mRNA has been reviewed previously [2–4]. Early work on the transcriptional regulation of these genes has also been reviewed [3,4].

CARBAMOYL-PHOSPHATE SYNTHASE I

CPS is an abundant protein in hepatocytes, accounting for about 20% of mitochondrial protein and roughly 5% of total liver protein [128–130]. The enzyme has been purified from bovine [131], rat [129,130,132] and human [133] liver, and seems to be present in a state of monomer-homodimer equilibrium [128,132,134]. cDNA clones have been isolated from rat [79,116,135] and human [79,136] liver. The predicted polypeptide length is 1500 amino acids for the precursor protein, with a mitochondrial N-terminal signal sequence of 38 or 39 amino acid residues [135,136]. The human CPS gene was mapped to the short arm of chromosome 2 [79]. The rat gene has been estimated to be approx. 110–120 kb long, and part of its structure determined [135]. This gene is mainly expressed in hepatocytes and epithelial cells of the intestinal mucosa [21]. Another type of CPS, named CPS II, which catalyses the first step of the pyrimidine biosynthetic pathway, is present ubiquitously in mammalian tissues. This enzyme is a part of a large trifunctional polypeptide of 2225 amino acids [137,138], called the CAD complex, which also contains the next two enzymes of the pathway, i.e. aspartate transcarbamylase and dihydro-orotase [139,140]. CPS II utilizes glutamine instead of ammonia as the nitrogen-donating substrate and does not require *N*-acetylglutamate for enzyme activity. Biochemical analysis and comparison of amino acid sequences suggests that ammonia-utilizing *N*-acetylglutamate-dependent CPS (CPS I) has evolved from CPS II via the glutamine-utilizing *N*-acetylglutamate-dependent form designated CPS III [141,142] that is involved in urea and/or arginine biosynthesis in some invertebrates and fish.

The 2.1 kb 5' region of the rat CPS gene exhibited liver-specific promoter activity in an *in vitro* transcription analysis using nuclear extracts of a hepatoma cell line (HepG2) and a cervical cancer cell line (HeLa) as a control [143]. On the other hand, liver-selectivity at a marginal level was observed with the 5' region from –597 to +1 bp in an *in vitro* transcription analysis using nuclear extracts of rat organs [144]. With these *in vitro* transcription systems, as well as with transient transfection systems using cultured hepatoma cell lines, at least three *cis* elements apparently required for maximum promoter activity were identified: a GA-rich sequence around –55 bp [145]; a palindromic GTTGCAAC sequence around –110 bp binding to C/EBP α [146,147] and possibly to another factor(s) [145] (Figure 2); and an unidentified element(s) between –160 and –1200 bp [146]. The element around –110 bp was suggested to act as an anti-repressor [145] by relieving the repressor activities of the two elements around –90 bp and –140 bp that also interact with C/EBP α [146,147] and possibly with another factor(s) [145]

Figure 2 Factors binding to regulatory regions of genes for the ornithine cycle enzymes

The transcription start site of each gene is indicated by the 'hooked' arrow. The enhancer regions were identified 11 kb upstream from the start site of the OTC gene and 11 kb downstream from the start site of the arginase gene. Liver-selective factors C/EBP and HNF-4 are shown in dark and light pink respectively. C/EBP represents several members of the C/EBP family. HNF-4 sites can be recognized also by COUP-TF and possibly by other factors. For further explanation, see the text.

(Figure 2). Three more upstream C/EBP α binding sites in the promoter region have been identified [147].

ORNITHINE TRANSCARBAMYLASE

OTC has been purified from bovine [148], rat [149,150] and human [151,152] liver, and proved to be a homotrimer. cDNA clones were isolated from rat [81,153,154], mouse [155] and

human [156] liver. The predicted polypeptide is composed of 322 amino acid residues for the mature portion, preceded by a mitochondrial signal sequence of 32 amino acid residues [81,153–156]. The human OTC gene is located on chromosome Xp21.1 [157]. The rat [158], mouse [159] and human [160] genes consist of 10 exons and span a region of 70–75 kb. The OTC gene is mainly expressed in hepatocytes and in epithelial cells of the intestinal mucosa [21,22].

Figure 3 Role and regulation of the OTC promoter and enhancer in the context of tissue-selective transcription

In transgenic mice, the OTC promoter exhibits higher activity in the small intestine than in the liver; the enhancer inverts this tissue-selectivity of the promoter, bringing about higher expression in the liver. The OTC promoter is activated by HNF-4, a liver- and small-intestine-selective member of the steroid receptor superfamily, and is competitively repressed by COUP-TF, a ubiquitous member of this family. For activation of the enhancer, the two liver-selective factors HNF-4 and C/EBP β are required, and neither alone is sufficient. This appears to enable these liver-selective, but not strictly liver-specific, factors to confer more restricted liver-specificity on expression of the target OTC gene.

Characteristically, OTC activity is little induced in primary cultured rat hepatocytes by glucocorticoid or by glucagon, in contrast to the other four ornithine cycle enzymes [112,113]. The mRNA level of OTC decreases rapidly and cannot be restored by either hormone in primary hepatocytes ([114]; M. Takiguchi and M. Mori, unpublished work). Rather, glucocorticoid lowers the mRNA level ([114]; M. Takiguchi and M. Mori, unpublished work).

Attention has been directed at the expression of the OTC gene from two points of view, i.e. X chromosome inactivation and/or methylation. In the liver of a mutant mouse in which the karyotype was ingeniously arranged, the OTC gene on the inactive X chromosome was shown to be derepressed with age [161]. Cultivation of rat hepatoma cells bearing no significant OTC activity in arginine-depleted and ornithine-supplemented medium allowed selection of OTC-producing cells [162]. The frequency of emergence of the OTC-producing cells was dramatically increased by treatment with 5-azacytidine, which causes DNA hypomethylation, suggesting that hypermethylation plays a role in the repression of the OTC gene in hepatoma cells [163,164]. In the mouse *Mus hortulanus*, CpG sites located 12 kb upstream from the OTC gene were shown to be hypomethylated in the liver compared with the kidney, exhibiting a correlation with the tissue-specificity of OTC gene expression [165]. These sites can be related to the liver-specific enhancer located 11 kb upstream from the OTC gene in the rat ([166,167]; see below). Several scaffold-associated regions were identified in the human OTC locus on both active and inactive X chromosomes [168].

Promoter and enhancer exhibiting differential organ specificity

Studies using transgenic mice revealed that the 1.3 kb promoter region of the rat gene [169] and the 0.7 kb region of the mouse gene [170] can conduct small-intestine-selective expression of the introduced genes at levels comparable with those of the endogenous OTC gene. However, in the liver the mRNA levels of the introduced genes were very low, thereby suggesting the presence of a liver-selective enhancer-like element(s) in addition to the promoter region. A subsequent search for such an element using a transient transfection system with the hepatoma cell line HepG2 revealed a hepatoma cell-selective enhancer located 11 kb upstream from the transcription start site of the rat gene [166] (Figures 2 and 3). Again with transgenic mice, this enhancer was

shown to function in a liver-specific manner: a 1.6 kb DNA fragment containing the enhancer region can invert the organ specificity of transcription from the linked OTC promoter, and lead to higher expression of the introduced gene in the liver than in the small intestine [167]. Therefore the OTC promoter and enhancer are preferentially active in the small intestine and the liver respectively (Figure 3); hence they can be regarded as discrete regulatory units, not only spatially but also functionally. This presents a typical model for mechanisms that enable transcription to be restricted to several discrete tissues. Expression of the OTC gene is regulated differentially in the liver and in the small intestine, nutritionally [32], hormonally [31] and developmentally [28,30,31]. It is likely that the OTC promoter and enhancer are differentially involved in this tissue-specific regulation.

Repression of the promoter by a ubiquitous transcriptional activator

In transient transfection analyses using HepG2 and non-hepatic cells, the 0.8 kb 5' region of the mouse gene [171] and the 1.3 kb region of the rat gene [166] exhibited HepG2-selective promoter activity. Within the approx. 220 bp promoter region of the rat gene there are at least one negative and two positive regulatory elements [166]. Both of the two positive elements around positions -105 and -25 can be bound by an identical set of two factors, HNF-4 and chicken ovalbumin upstream promoter-transcription factor (COUP-TF) [172]. Both HNF-4 [46] and COUP-TF [173] are orphan members of the steroid receptor superfamily. HNF-4 mRNA is present selectively in the liver, intestine and kidney [46], while COUP-TF mRNA exhibits a rather ubiquitous tissue distribution (Ear3 mRNA in [174]). These two factors recognize direct repeats of a heptamer nucleotide sequence [172,175-178], which can also be recognized by other steroid receptor superfamily members such as apoA1 regulatory protein (ARP-1), retinoic acid receptors, retinoid X receptors and peroxisome-proliferator-activated receptors (PPARs) [177-181]. These factors bind to target DNA sequences as a homodimer and/or a heterodimer. Therefore a complicated mass of dimeric species may interact with the target heptamer repeats.

In co-transfection experiments, HNF-4 stimulated transcription from the OTC promoter [172]; hence this factor is likely to be involved in tissue-selective activation of the OTC gene in the liver and intestine. On the other hand, COUP-TF repressed the OTC promoter, whereas it can activate several other promoters [172]. Therefore COUP-TF is potentially a dual regulatory factor and might be involved in repression of the OTC gene in tissues other than the liver and intestine (Figure 3). If this is the case, it means that repression of a tissue-specific gene in non-expressing tissues can be achieved without requiring a factor specialized in repression.

Determination of the liver-specificity of the enhancer by combinatorial operation of two liver-selective factors

In the essential minimum approx. 110 bp region of the OTC enhancer, there are two sites binding with HNF-4 and two sites binding with C/EBP family members [166,167,172]. The enhancer activity could be reconstituted by concatemerization of a fragment containing one HNF-4 site and one C/EBP site, but not by concatemerization of either single site [167]. In co-transfection experiments using a non-hepatic cell line, the reconstituted enhancer was activated by a combination of HNF-4 and C/EBP β , but not by either alone [167] (Figure 3). Both HNF-4 and C/EBP β are liver-selective, but not strictly liver-specific. There-

fore it seems unlikely that the presence of one of these factors can determine by itself the liver-specificity of target genes. However, if combination of these factors is considered, the number of tissues that express both factors is more restricted. Taken together with the observation that the combinatorial operation of both HNF-4 and C/EBP β is a prerequisite for activation of the OTC enhancer, light is shed on the mechanism that enables liver-selective but not strictly liver-specific factors to confer more restricted liver-specificity on transcription of the OTC gene.

ARGININOSUCCINATE SYNTHASE

AS was purified from rat [182], bovine [183] and human [184,185] liver and human lymphoblasts [186], and proved to be a homotetramer. cDNA clones were originally isolated from an AS-overproducing human squamous carcinoma cell line [187,188], and later from rat kidney [189], and from mouse [190] and bovine [191] liver. The predicted polypeptide is composed of 412 amino acid residues [188–191]. The human AS gene was mapped to chromosome 9q34 [192,193], and the mouse gene to chromosome 2 [194]. The human gene spans a 63 kb region [195]. The human and mouse AS genes contain 16 exons [190]. In the human genome, 14 pseudogenes were identified [196,197]. This enzyme is expressed in a number of tissues [25,27], with highest expression in the liver, proximal tubules of the kidney [13,23,24] and testis [25].

Non-hepatic AS is involved in arginine biosynthesis. Culturing cells in a medium lacking arginine leads to an increase in AS expression [187,198–200], although this effect may not be arginine-specific and can also be caused by leucine starvation [201]. In cells resistant to the toxic arginine analogue canavanine, AS expression is also increased [187,200,202]. These up-regulations of AS expression are caused mainly by transcriptional activation [201,203]. Investigations of *cis*-acting elements responsible for activation have been performed using the human squamous cell carcinoma cell line RPMI 2650 (reviewed in the introduction of [201]). An element(s) mediating the regulation by arginine seems to reside in the 5' flanking region up to –149 bp and/or in the intragenic region [201,204,205]. On the other hand, the element responsible for the up-regulation in canavanine-resistant cells has not been identified within the region from –3 kb to +9 kb [204,205], while a possibility was suggested that the mature mRNA-coding region is involved in interactions with a positive *trans* factor(s) [203,206].

In the promoter region of the AS gene, three sites binding with Sp1 [207] were detected [208] (Figure 2). They co-operatively stimulate AS promoter activity, and appear to be involved in basal level expression of the gene in various tissues.

ARGININOSUCCINATE LYASE

AL was purified from bovine [209] and human [210,211] liver, and proved to be a homotetramer. cDNA clones were isolated from rat [212,213] and human [214–216] liver. The predicted polypeptide is composed of 461 and 464 amino acid residues in the rat [213] and human [215,216] respectively. The human AL gene was mapped to chromosome 7cen-q11.2 [214,216]. The rat [217] and human [218] genes are approx. 14 kb and 35 kb long respectively, and consist of 16 exons. The chicken AL gene (also designated the δ 2-crystallin gene; see below) is about 9 kb long and consists of 17 exons [219]. The tissue distribution of AL in mammals resembles that of AS; expression in the liver, proximal tubules of the kidney [13,23,24] and testis [25] is prominent, compared with lower ubiquitous expression in many other tissues [25,26].

In transient transfection analysis, the 5' region up to –235 bp of the rat AL gene exhibited comparable levels of promoter activity in all cell lines tested, with no obvious liver cell specificity [220]. This appears to be a reflection of the ubiquitous expression of the gene, and might imply the presence of a remote enhancer-like element that is responsible for high expression in the liver. In the promoter region, two protein binding sites were detected (Figure 2): a site for Sp1 around –60 bp and a site for NF-Y [221,222] around –80 bp, which overlaps with a positive *cis* regulatory element. NF-Y, also designated CBF [223,224], is a ubiquitous transcription factor that consists of two or more different subunits [222,225,226] and recognizes the CCAAT box sequence. Interestingly, the NF-Y binding site of the AL promoter contains the sequence element CCAATTGG, which can be regarded as a dyad-symmetry of the CCAAT motif. The intactness of the correctly spaced two half-site motifs was a prerequisite for binding with NF-Y, suggesting that NF-Y sites generally possess dyad-symmetrical features [220].

The AL gene in birds and reptiles provides an example of the recruitment of enzyme-encoding genes as taxon-specific crystallin genes (reviewed in [227,228]). Crystallins are major structural proteins present in the transparent eye lens. In the evolutionary course to birds and reptiles, the AL gene was duplicated, yielding a tandem array of two genes. One gene remained to encode the enzyme protein of AL, while the other gene was specialized to encode δ -crystallin. The latter gene is designated the δ 1-crystallin gene [229,230], and the former gene was initially named the δ 2-crystallin gene [219]. In chickens [231] and ducks [232], only the δ 2 gene-encoded protein exhibits AL enzyme activity. In the lens of 14-day-old chicken embryos, δ 1-crystallin mRNA is abundant; the mRNA level of AL/ δ 2-crystallin is 1–2% of that of δ 1-crystallin [233–235]. On the other hand, in the lens of the embryonic duck [236] and in cultured cells of the chicken embryonic lens [237], the δ 1 and AL/ δ 2 genes appear to be expressed at comparable levels. Both the δ 1 and AL/ δ 2 mRNA levels in the chicken lens decrease after hatching; this occurs to a greater extent for δ 1 than for AL/ δ 2, leading to relatively higher levels of AL/ δ 2 mRNA than δ 1 mRNA in 1-year-old chickens [235]. In non-ocular tissues of chickens, the δ 1 and AL/ δ 2 genes are expressed at low levels, and AL/ δ 2 mRNA is more abundant than δ 1 mRNA, especially in adults [234,235]. Promoters of both the δ 1 [238] and AL/ δ 2 [234] genes exhibit no apparent lens cell specificity in transient transfection analyses using primary cultured chicken embryonic cells. A lens-cell-specific enhancer was detected in intron 3 of the δ 1 gene [238] and characterized [239,240]. Intron 3 of the AL/ δ 2 gene shows high sequence identity with that of the δ 1 gene, and was also reported to exhibit lens-cell-specific enhancer activity [234].

ARGINASE

Arginase was purified from a number of sources, including rat [88,241,242], mouse [243], rabbit [244] and human [245,246] liver, and is a homotrimer [247,248]. cDNA clones were isolated from rat [123,249] and human [250,251] liver. The predicted polypeptide is composed of 323 and 322 amino acid residues in the rat [249] and human [251] respectively. The human arginase gene was mapped to chromosome 6q23 [252]. The rat [253] and human [254] genes are approx. 12 kb and 11.5 kb long respectively, and consist of 8 exons. Besides 'liver-type' arginase, which is involved in the ornithine cycle, the presence of an isoenzyme(s) in non-hepatic tissues has been reported [255–258]. Recently three different forms of non-hepatic arginase cDNAs in *Xenopus laevis* were cloned [259].

The 5' region of the rat liver-type arginase gene from –193 to

Figure 4 Hypothetical mechanism for the secondary response of the arginase gene to glucocorticoid

(a) The primary and secondary responses of the gene to glucocorticoid. The primary response is caused directly by the glucocorticoid-receptor complex, shown by the triangle and oval. The secondary response is mediated by a newly synthesized factor(s) (in light pink) through the primary response. (b) The C/EBP family members interacting with the enhancer region located around intron 7 of the arginase gene are candidates for factors mediating the secondary response of the gene.

+286 bp exhibited a moderately liver-selective promoter activity in an *in vitro* transcription analysis using nuclear extracts of rat liver and brain [260]. 5' deletion analysis revealed a positive regulatory element around the region from -90 to -51 bp. Overlapping with this region, two protein-binding sites were detected (Figure 2); the more upstream site around -90 bp binds C/EBP-related factors, and the more downstream site around -60 bp is recognized, in a mutually exclusive manner, by two factors each related to CTF/NF-1 [261] and Sp1. Another site binding the CTF/NF-1-related factor was detected around +100 bp.

The mRNA levels for arginase and other ornithine cycle enzymes, except for OTC, increase in response to glucocorticoid and glucagon, as described above. This mRNA accumulation appears to be led, at least in part, by transcriptional activation [87,115]. However, in most cases, the mechanisms of transcriptional activation by these hormones remain to be determined. A characteristic feature of the induction of ornithine cycle enzyme genes by glucocorticoid is that induction is caused in a 'secondary' manner [114]. The 'primary' response to glucocorticoid is brought about by binding of the hormone-receptor complex to regulatory sequences of target genes (Figure 4a). mRNA induction in the primary response is rapid and insensitive to protein synthesis inhibitors, since *de novo* polypeptide synthesis is not required prior to transcription of the target genes. On the other hand, the secondary response seems to be mediated by a transcription factor(s) that is synthesized *de novo* through the primary response. mRNA accumulation in the secondary response follows a relatively delayed time course, typically requiring a time lag of several hours, and is sensitive to protein synthesis inhibitors.

Recently the regulatory mechanism for the induction of the rat arginase gene by glucocorticoid was addressed. Transient transfection analysis using the rat hepatoma cell line H4IIE revealed an enhancer region that exhibits glucocorticoid responsiveness, as well as hepatoma cell selectivity [262]. This enhancer region resides in an approx. 200 bp segment around intron 7, located 11 kb downstream from the transcription start site. Induction of a reporter gene under the control of the arginase enhancer exhibited a delayed time course compared with that under the control of the mouse mammary tumour virus promoter, which shows typical primary glucocorticoid responsiveness [263]. Therefore

the arginase enhancer seems to mediate the secondary glucocorticoid response. Four protein binding sites were detected in this enhancer region, two of which are recognized by C/EBP family members such as C/EBP α and C/EBP β . The C/EBP β gene in cultured rat hepatocytes was shown to be induced primarily by glucocorticoid (F. Matsuno, unpublished work). Induction of C/EBP β mRNA by glucocorticoid in a hepatoma cell line has also been reported [264,265]. Besides the liver, studies on adipoblasts and adipocytes [35,266] have shown that the C/EBP δ gene is primarily induced by glucocorticoid in these cells. Therefore the C/EBP family members can be regarded as candidates for factors that mediate the secondary response of the arginase gene (Figure 4b). The availability of C/EBP β /NF-IL6 gene-disrupted mice [267] will facilitate the analysis of the role of this factor in the regulation of ornithine cycle enzymes.

CONCLUDING REMARKS AND PERSPECTIVES

The complete set of genes for the five ornithine cycle enzymes are predominantly expressed only in the liver. Genes for the initial two enzymes, CPS and OTC, are also expressed in the intestine, and genes for the next two enzymes, AS and AL, in the kidney and testis, as well as at lower levels in many other tissues. The promoter regions of CPS, OTC and the final enzyme, arginase, seem to possess the potential to conduct liver-selective transcription. This was verified, as for the OTC promoter, using transgenic mice. However, the OTC promoter was more active in the small intestine than in the liver. An enhancer located far upstream of the gene can invert this tissue specificity of the promoter, bringing about greater expression in the liver than in the small intestine. Determination of the liver and small intestine specificity of the promoter appears to involve competition between a tissue-selective transcription factor HNF-4 and a ubiquitous factor COUP-TF. On the other hand, the combinatorial operation of the two liver-selective factors HNF-4 and C/EBP β is likely to be important in determining the liver specificity of the enhancer. These hypotheses on the regulatory mechanisms of the OTC gene require further investigation, especially in the context of developmental processes.

The promoter regions of the AS and AL genes show features characteristic of ubiquitously expressed genes, apparently reflecting the expression of these genes at low levels in a number of

tissues. Remote enhancer-like regions that conduct tissue-selective high-level transcription might exist, and remain to be discovered. As for the AS gene, a *cis*-element(s) responsible for high-level transcription in canavanine-resistant cells might also exist. Mechanisms for the regulation of this gene by arginine, a unique phenomenon resembling metabolite regulation, will be further clarified by delimitation of the *cis*-regulatory region and by identification of *trans*-acting factors. Induction of AS mRNA, in co-ordination with iNOS mRNA, by lipopolysaccharide and interferon- γ is likely to involve transcriptional activation.

The developmental and nutritional regulation of the ornithine cycle enzyme genes seems to be mediated by hormones such as glucagon and glucocorticoid. mRNA accumulation in response to these hormones is presumably caused, at least in part, by transcriptional activation. A characteristic feature of the induction of the ornithine cycle enzyme mRNAs by glucocorticoid is that induction is due to a secondary response, which seems to be mediated by a protein factor(s) synthesized *de novo* through the primary response to the hormone. An enhancer region with glucocorticoid responsiveness of an apparently secondary type was detected around intron 7 of the rat arginase gene. C/EBP family members that interact with this enhancer region might mediate the secondary response of the arginase gene.

The genes of the five ornithine cycle enzymes are regulated generally in a co-ordinated manner, both developmentally and nutritionally. Therefore a shared transcription factor(s) might be involved in this co-ordinated regulation. A common 13-nucleotide sequence element was detected in the promoter regions of four of the ornithine cycle enzyme genes [218,253,268], as well as in that of the gene for a related enzyme, ornithine aminotransferase [268–271]. This element, termed the urea cycle element [268], remains to be analysed for its function. At present the most likely candidates for factors involved in the co-ordinated regulation seem to be C/EBP family members, which interact with regulatory regions of three ornithine cycle enzyme genes. It is noteworthy that C/EBP family members interact with the arginase enhancer that mediates the response to glucocorticoid causing co-ordinated up-regulation of the cycle.

Note added in proof (received 10 October 1995)

After this Review was submitted, detection of the 10 kb upstream enhancer of the rat CPS gene was reported [272].

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