



## The Endocrine Regulation of Chicken Growth

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**ABSTRACT :** The somatotrophic axis plays a key role in proliferation and differentiation of avian organs during both pre- and post-hatching periods. This review discusses the complexity of regulation of the endocrine system for chicken development and growth by growth hormone (GH), insulin-like growth factor (IGF), and IGF binding protein (IGFBP). In addition, the thyrotrophic axis, including thyrotropin-releasing hormone (TRH) and thyroid hormones ( $T_4$  and  $T_3$ ), is also involved in the GH-secreting pattern. In mammals, IGF-I and -II are always sequestered in a 150 kDa non-covalent ternary complex. This complex consists of one molecule each of IGF-I or IGF-II, IGFBP-3 or IGFBP-5 and an acid labile subunit (ALS). Chick ALS is identified in different strains for the first time, and further investigation of the expression of ALS on developmental stage and ALS effect on IGF bioavailability may be addressed in the future. (**Key Words :** Chicken, Growth, GH, IGF-I, IGFBP, ALS)

### INTRODUCTION

A demonstration of the endocrine system for development and growth in poultry is less well understood than in mammals. In general, growth is a complicated reaction of metabolic and physiological effects involving the endocrine controlling systems, genetic regulations, nutritional levels and environmental factors. Avian development is known as five classified stages such as embryonic, posthatch, juvenile, pubertal, and adult (Cogburn et al., 2000). Sigmodial "S-type" growth curve has been described for numerous avian species including chicken and turkey. The highest growth rate of domestic chicken occurs during the late embryonic through juvenile stages of development (Cogburn et al., 2000; Kuhn et al., 2002).

The endocrine factors that regulate growth and development affect different regulatory axes and participate in each stage of growth (De Groef et al., 2008; Scanes, 2009). The somatotrophic axis of chicken is regulated by growth hormone-releasing hormone (GHRH), thyrotropin-releasing hormone (TRH) and somatostatin, which control secretion of growth hormone (GH) from the anterior pituitary gland (Porter, 2005; Kuhn et al., 2005). GH as a

somatotropic activator exerts two types of action. GH acts directly on development and metabolism. Indirectly, GH binds GH receptor (GHR) on the membrane of liver and then activates hepatic insulin-like growth factor-I (IGF-I) secretion, which stimulates the differentiation and proliferation of bone and muscle cells (McMurtry et al., 1997; Kuhn et al., 2002). In the vascular system, most of IGF circulate in ternary complexes composed of one molecule each of IGF, IGF binding protein (IGFBP) and acid labile subunit (ALS) (Kim and Boisclair, 2008). Although, the action of IGF-II during chicken development and growth has not been established, and is not under direct control of the somatotrophic axis, IGF-II has a high affinity for IGF-I receptor and may regulate endocrine and paracrine effects on chicken growth (Duclos and Goddard, 1990; Armstrong and Hogg, 1994). In this review, I present endocrine effects on chicken development and growth based on the current knowledge.

### SOMATOTROPIC AND THYROTROPIC AXES

Somatotrophs are one of five cell types within the pituitary gland and their major function is the secretion of GH. The abundance of GH-secreting cells increases dramatically between embryonic day 12 and 16 (Frawley et al., 1985). Plasma GH is detectable after embryonic day 16 and most of somatotrophs respond to GHRH and somatostatin (Porter et al., 1995; Dean et al., 1997; Piper

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and Porter, 1997). TRH-secreting cells appear at embryonic day 5 (Thommes et al., 1983). Both TRH and somatostatin are also detectable by radioimmunoassay in thyrotrophs at embryonic day 14 (Harvey et al., 1979). Toward the end of embryonic development, TRH levels increases progressively, but somatostatin levels remain stable at embryonic day 17 and double at hatching (Geris et al., 1998). GH release from isolated pituitaries of 18-day-old has been observed by administration of TRH or GHRH, but not 14-day-old embryos (Darras et al., 1994). Prior to hatching, a steep increase in plasma GH occurs (Figure 1; Harvey et al., 1979). Thus, these results represent the somatotrophs appear to become fully responsive to TRH and GHRH after embryonic day 16.

Plasma GH levels increase steeply between 3 and 4 weeks of age and then abruptly decrease to the low levels in puberty and adult (Goddard et al., 1988; Johnson et al., 1990; McGuinness and Cogburn, 1990; Burnside and Cogburn, 1992; McCann-Levorsse et al., 1993). The hepatic GHR is transiently expressed at embryonic day 17 (Cogburn et al., 2000). After hatching, hepatic GHR mRNA progressively increases until a peak reached at puberty (Burnside and Cogburn, 1992). However, an administration of chicken GH between embryonic day 14 and 20 fails to stimulate to IGF-I production in the liver of chick embryos (Huybrechts et al., 1985). In addition, compared between embryos which have a deficient hepatic GHR and normal embryos, there is no difference in IGF-I levels. This may explain the almost identical body weight at hatching between normal and dwarf chick (Huybrechts et al., 1989). This evidence indicate that IGF-I secretion seems to not depend on GH during embryonic period, as it is not in mammals.

The onset of GH-dependent growth is identified by activation of the somatotrophic axis as indicated by increase in circulating GH, hepatic GHR mRNA and plasma IGF-I

levels. However, throughout development and growth, circulating GH levels are inversely related to hepatic GH binding and GHR expression (Figure 1; Burnside and Cogburn, 1992; Cogburn et al., 2000; Kuhn et al., 2002). The hepatic GH binding of turkeys has also been inversely related to plasma GH levels (Vasilatos-Younken et al., 1990). Several studies support the down-regulation of the GHR by GH. In hypophysectomized chicks, plasma GH levels reduce below the detection limit but hepatic GH binding and GHR expression are increased. Moreover, the GHR increase by hypophysectomy is normalized by GH administration (Vanderpooten et al., 1991b). Rapid growing rate in chicken and turkey is also related to lower GH levels and higher GH binding (Vasilatos-Younken et al., 1988; Vanderpooten et al., 1993). Dwarf chicken which is lacking the GHR show no hepatic GH binding but circulating plasma GH is increased (Scanes et al., 1983; Kuhn et al., 1989; Vanderpooten et al., 1991a). Although the exact factors regulating GHR synthesis is unknown, we speculate that GH down regulates GHR expression either directly or by IGF-I induction, and up regulates internalization of GH-GHR complex into the cells. The chick GHR gene has been partially characterized (Burnside et al., 1991; Agarwal et al., 1994). The coding exons have a homolog in the human GHR. Heterogeneity in the 5'-UTR of GHR transcript is found and two 5'-UTRs are observed in chicken GHR transcripts (Edens and Talamantes, 1998). Chicken GHR isoforms are generated by alternative RNA cleavage/polyadenylation and alternative splicing in intron 6/7 position (Oldham et al., 1993).

In chicken, the thyrotrophic axis has profound developmental effects which are intimately tied to the somatotrophic axis. The predominant form of thyroid hormone (TH) secreted by the thyroid gland is thyroxine ( $T_4$ ). Triiodothyronine ( $T_3$ ) is an active form and is derived from hepatic monodeiodination of  $T_4$  by 5'D-I

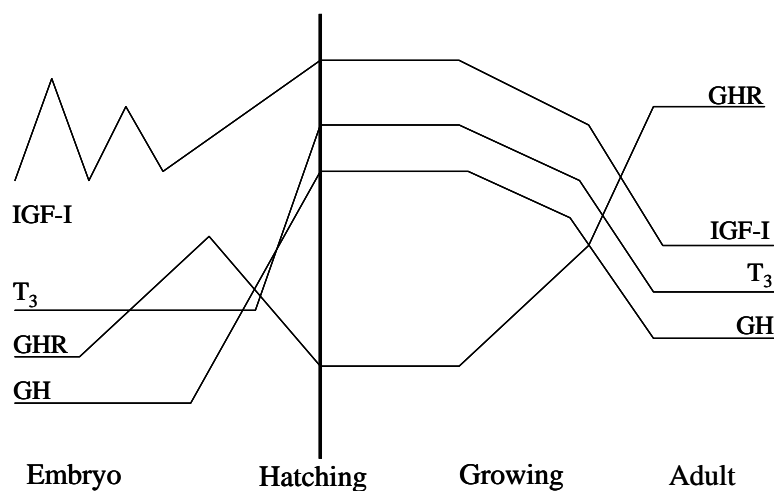


Figure 1. Developmental pattern of GH, IGF-I,  $T_3$ , GHR in the chicken (modified from Kuhn et al., 2002).

monodeiodinase (D-I), whereas both  $T_4$  and  $T_3$  are catabolized to metabolically inactive reverse  $T_3$  ( $rT_3$ ) and  $T_2$  by 5D-III deiodinase (D-III) (Figure 2). Thyroid hormones are essential for normal growth in chicken since thyroidectomy results in significant decrease in growth rate (King and King, 1976; Moore et al., 1984), and this effect can be normalized by  $T_3$  or  $T_4$  administration (King and King, 1973). Growth rate is reduced in chicken following goitrogen administration (Rosebrough and McMurtry, 2003). Moreover, goitrogen decreases circulating IGF-I levels and hepatic IGF-I mRNA which are restored by  $T_4$  administration (Tsukada et al., 1998). Growth is partially restored by  $T_3$  replacement therapy in hypophysectomized chicks (Scanes et al., 1986). Dwarf chickens which show no GHR are also associated with decreased plasma  $T_3$  levels. Furthermore,  $T_3$  administration can partially restore growth (Leung et al., 1984; Marsh et al., 1984; Scanes et al., 1986). Thus, the normal growth rate partially depends on circulating  $T_3$  levels.

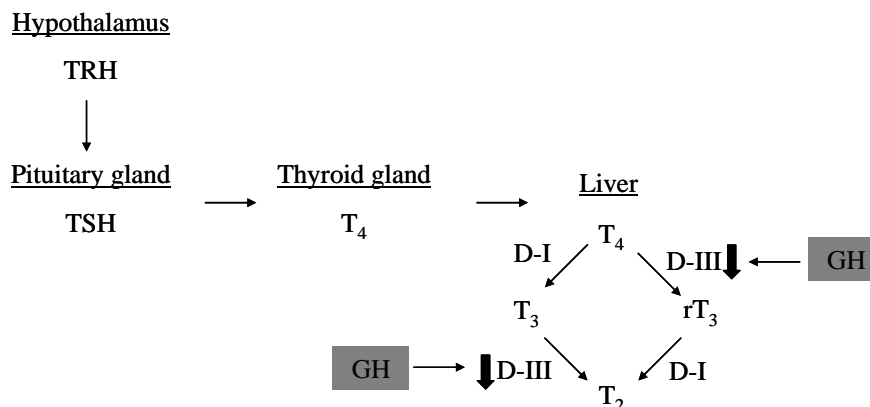
GH administration increases circulating  $T_3$  and decreases plasma  $T_4$  in chickens (Vasilatos-Younken et al., 1999; Kuhn et al., 2002). This effect shows that GH has no effect on D-I activity but decreases hepatic D-III activity. Thus, the increase in plasma  $T_3$  by GH stimulation is not due to an elevated  $T_3$  production, but the result of a suppressed  $T_3$  degradation (Figure 2). TRH administration increases both plasma  $T_3$  and  $T_4$  in chicken embryo and growing chicken (Kuhn, 1993; Kuhn et al., 2002). TRH-induced increase in plasma  $T_3$  may also be related to a down regulation of D-III by GH, which is simultaneously released. In dwarf chicken, which has no functional hepatic GHR, plasma levels of GH and  $T_4$  are elevated, while plasma  $T_3$  and IGF-I levels are depressed (Scanes et al., 1983; Huybrechts et al., 1989). This indicates impaired  $T_4$  conversion into metabolically active  $T_3$ , which is regulated by GH.

The stimulatory effect of TH on the growing chicken

can be mediated either by increases in circulating IGF-I levels or by direct effects of  $T_3$  on the growing tissues (Vasilatos-Younken et al., 1999; Kuhn et al., 2002).  $T_3$  stimulates cartilage in the chick embryo (Burch and Lebovitz, 1982; Burch and Van Wyk, 1987). Dietary  $T_3$  treatment reduces accumulation of excess body fat and increases accretion of muscle protein (Cogburn, 1991; Cogburn et al., 1995). Moreover, the synergic effect of  $T_3$  and GH treatment is observed in improving body composition of broiler (Cogburn, 1991; Cogburn et al., 1995).

### INSULIN-LIKE GROWTH FACTOR AXIS

In general, IGF-I and -II are regulating factors of proliferation, differentiation and growth of tissues. Two IGFs are very similar peptides of approximately 7 kDa and similar to insulin in structure. Although IGFs are predominantly produced in the liver, these factors are also produced ubiquitously and exert paracrine/autocrine effects. The existence of IGFs in chickens has been identified by a number of early studies (Haselbacher et al., 1980; Wilson and Hintz, 1982; Daughaday et al., 1985). Purification of IGF-I and -II from chicken serum and the amino acid sequence deduced from cDNA indicate that the difference of 8 amino acids presents in IGF-I, and 13 amino acids in IGF-II, when compared to human IGFs (Ballard et al., 1990; Kallincos et al., 1990). In chicken, the expression of IGF-I increases dramatically between embryonic day 3 and 8 (Serrano et al., 1990). Circulating IGF-I can be detected as early as embryonic day 6, increases until a peak is reached between embryonic day 14 and 18 and decreases before hatching (Serrano et al., 1990; Kikuchi et al., 1991; De Pablo et al., 1993). However, the absence of detectable hepatic IGF-I mRNA and the presence of plasma IGF-I before the onset of GH secretion suggest that circulating IGF-I could be derived from an extra-hepatic origin and



**Figure 2.** Interaction of GH and TH for deiodinases activity. D-I, 5'D-I monodeiodinase; D-III, 5D-III deiodinase (modified from Vasilatos-Younken et al., 1999).

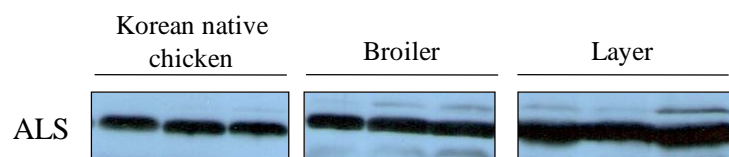
IGF-I synthesis is GH-independent during embryogenesis (Serrano et al., 1990; Kikuchi et al., 1991; Tanaka et al., 1996). The average concentration of IGF-I and IGF-II in embryonic stage is 5-20 and 75-120 ng/ml, respectively (McMurtry et al., 1997). After hatching, circulating hepatic IGF-I levels increase sharply, reach a plateau between 3 and 7 weeks of age, and gradually decline to basal levels by puberty (McCuinness and Cogburn, 1990; Kikuchi et al., 1991; Burnside and Cogburn, 1992). In mammals, plasma IGF-II levels is 2-3 fold higher than IGF-I after birth, but, in chickens, two IGFs show similar levels after hatching (McMurtry et al., 1997).

In mammals, two distinct IGF-binding receptors exist with high affinity for IGF-I and -II. However, in chickens, the IGF-II receptor (cation-independent mannose-6-phosphate receptor) is present, but it does not bind IGF-II, indicating that the effects of IGF-II are mediated via the IGF-I receptor (Yang et al., 1991; Zhou et al., 1995). Both IGF-I and IGF-II can associate with only IGF-I receptor to regulate the physiological actions. IGF-I receptor has been identified in chick embryo as well as in tissue derived from embryo (De Pablo et al., 1993). IGF-I receptor is present in brain, muscle and liver of chick embryo (Armstrong and Hogg, 1994). It is surprising that the highest abundance of IGF-I receptor is found in brain. This reflects that IGF-I receptor may have a role in central nervous development in chick embryo (Armstrong and Hogg, 1994; Holzenberger et al., 1996). After hatching, the hepatic IGF-I receptor levels sharply increase, reach a peak at 1 week of age, and reduce to low levels by 3 weeks of age (Bassas et al., 1987; Duclos and Goddard, 1990; Duclos et al., 1991). Furthermore, the developmental increase in IGF-I receptor activity corresponds to peak levels of circulating IGF-I after hatching (Figure 1).

The stimulatory effects of IGF-I on development and growth appear to be mediated by the somatotrophic axis. In several *in vitro* studies, IGF-I and IGF-II promote the proliferation of preadipocytes, chondrocytes and fibroblasts (Cynober et al., 1985; Butterwith and Goddard, 1991; Leach and Rosselot, 1992). Moreover, in fibroblasts, IGF-I and IGF-II increase net protein accretion (Caldes et al., 1991). GH treatment in chicken hepatocytes induces IGF-I production (O'Neill et al., 1990). The secretion of IGF-I is tightly coupled to the pulsatile pattern of circulating GH. In GH administration with either pulsatile or continuous manner of 8-week-old chicks, plasma IGF-I is dramatically higher in the pulsatile than in continuous manner (Vasilatos-Younken et al., 1988). However, no changes in circulating IGF-I have been observed with GH administration in 3-week-old chicks (Cogburn et al., 1989; Rosselot et al., 1995), suggesting that the down regulation of hepatic GHR or uncoupling of GH signaling appears to be involved when circulating IGF-I levels are high in 3-week-old chicks (Mao

et al., 1997). Circulating IGF-I levels are reduced by 35-50% in hypophysectomized chickens (Scanes et al., 1986; Vanderpooten et al., 1991b), but either GH or TH replacement fails to restore IGF-I levels (Lazarus and Scanes, 1988; Proudman et al., 1994). This reflects that endocrine factors other than GH and TH may be responsible for maintaining IGF-I secretion. In dwarf chicken lacking the GHR, reduced body weight and long bone growth are associated with low levels of circulating IGF-I (Huybrechts et al., 1985), and IGF-I administration increases growth in an additive manner with T<sub>3</sub> (Huybrechts et al., 1985; Tixier-Boichard et al., 1992). Moreover, IGF-I administration also increases skeletal muscle by reducing protein degradation and increasing protein synthesis (Tomas et al., 1998; Conlon and Kita, 2002).

In mammals, six well characterized IGFBPs have been observed. These IGFBPs play a role in modulation of IGFs action by preventing insulin-like effects, regulation of half-life of IGFs in circulation, association with IGFs as carrier proteins and redistribution of IGFs between tissues and extracellular fluids. In addition, IGF-independent regulation of growth by IGFBPs in various cell types has been reported and these actions include effects on cell growth, apoptosis and cell migration (Mohan and Baylink, 2002). So far, five IGFBPs (IGFBP-1, 2, 3, 4, 5) and low-affinity IGFBP-7 are identified in NCBI chicken genome (build 2.1), since no IGFBP-6 gene homologue has been identified for chickens. The 30 kDa IGFBP corresponding to IGFBP-2 found in mammals is regulated by nutrition and developmental stage (Yang et al., 1993; Kita et al., 1996; Morishita et al., 1996; Kita et al., 2002). This IGFBP-2 is increased in hypophysectomized chicks and GH administration reduces IGFBP-2 levels (Morishita et al., 1993). The 22 kDa IGFBP as determined by ligand blotting is homologous with mammalian IGFBP-2 has a peak in 1 day after hatching and decreases between 3 and 24 weeks. Both 28 and 36 kDa are likely equivalent to mammalian IGFBP-3 and gradually increase after hatching, reach a peak at 5 weeks and decrease by 24 weeks (Radecki et al., 1997). In Korean native ogol chicken, IGFBP-2 is identified by ligand blotting, and increase after hatching between 3 and 7 weeks (Yun et al., 2005). Recently, IGFBP-2, -3 -5 and -7 are detected by the real-time PCR technique in broiler chickens (Leach et al., 2006; Lu et al., 2010). IGFBP-2, -3, -5 and -7 are found in both proliferative and hypertrophic chondrocytes, but IGFBP- and -4 are not expressed (Leach et al., 2006). In epiphyseal cartilage during development of broiler chickens, IGFBP-2 mRNA transiently reaches a peak between embryonic day 12 and 18, and gradually decreases by 42 weeks after hatching, suggesting IGFBP-2 may negatively affect tibia growth after hatching. IGFBP-3 mRNA is positively correlated with IGF-I and appears to modulate a down-regulation of



**Figure 3.** Detection of ALS in broiler, layer and Korean native chicken. Plasma samples were collected at 3 week of age for broiler and 40 week of age for layer and Korean native chicken. Plasma (0.5  $\mu$ l) from the indicated samples was electrophoresed on a 10% reducing SDS-polyacrylamide gel. After electroblotting, the membranes were incubated with bovine ALS antiserum 1082.

chicken tibia growth after hatching. IGFBP-5 mRNA is positively correlated with IGF-I in embryonic stage but is negatively correlated after hatching. Although some progress has been made in elucidating the identity and the expression of chicken IGFbps, much remains to be solved regarding the physiological modulation and action on chicken development and growth.

### ACID LABILE SUBUNIT (ALS)

ALS in most species has a molecular weight of 84-86 kDa, and is found as a 150 kDa noncovalent complex in the vascular compartment. This complex consists of one molecule each of IGFs, IGFBP-3 or 5 and ALS (Kim and Boisclair, 2008). In mammals, the structure of ALS gene is composed of 2 exons separated by 1 intron, and spans ~3.3 kb. The cDNA structure is conserved in sheep, cattle, human, pig and mouse (Dai and Baxter, 1992; Leong et al., 1992; Boisclair et al., 1996; Lee et al., 2001; Kim et al., 2006). 3D-structure predicted by computational modeling and rotary shadowing electron microscopy shows that ALS is a donut-shaped structure with negative-charged internal face which is thought to be important for binding with IGFBP-3 and -5 (Firth et al., 1998; Twigg et al., 1998; Janosi et al., 1999). ALS mRNA is predominantly detected in liver as well as in kidney, ovary and spleen (Dai and Baxter, 1994; Rhoads et al., 2000; Ueki et al., 2000). In cattle, the abundance of ALS mRNA is five-fold in liver than in lung, small intestine, adipose tissue, kidney and heart, but was almost absent in muscle and brain (Kim et al., 2006). ALS can be detected at 20 day-old embryo of rats (Chin et al., 1994) at 130 day-old fetus of sheep (Butler and Gluckman, 1986; Rhoads, et al., 2000) and 75 day-old fetus of pigs (Lee et al., 2001). ALS is synthesized in a GH-dependent manner (Ooi et al., 1998). GH binds the GHR on the membrane of liver, and then leads to the activation of Janus Kinase 2 (JAK2). JAK2 associates with the GHR following by JAK2 autophosphorylation as well as GHR phosphorylation. Phosphorylated JAK2 also phosphorylates STAT5 on a single tyrosine residue and induces STAT5 dimer which translocates into the nucleus and binds cis-elements in the promoter region of ALS gene (Ooi et al., 1998; Woelfle and Rotwein, 2004).

Incorporation of ALS in ternary complexes extends their

half-lives from 10 min (free IGFs) or 30 min (IGF-IGFBPs in binary complexes) to over 15 h (Zapf et al., 1986; Twigg and Baxter, 1998). This evidence explains that IGFs cross the endothelial barrier when in free form or binary complexes, but are unable to do when in ternary complexes (Binoux and Hossenlopp, 1988). To understand the functionality and the action of ALS on development and growth, ALS knock-out mice model has been studied (Ueki et al., 2000). ALS deficient mice show a reduction of circulating IGF-I (62%) and IGFBP-3 (88%), and suffer at 15% growth retardation, but have normal plasma levels of glucose, insulin and GH. GH replacement therapy can't restore in plasma IGF-I levels and growth (Ueki et al., 2009). This reflects that the ternary complexes are unable to be formed in ALS deficient mice and without ALS, overall IGF-I effects on development and growth is reduced.

Most previous studies for ALS have been conducted in mammals. Our laboratory recently identified ALS sequence in NCBI chicken genome (build 2.1). The cDNA and amino acid sequences were analyzed with Vector NTI software (ver. 9.0.0, InforMax). The ALS gene is located on chromosome 14 in chicken. The chicken ALS cDNA has a homology with human (75.5%) and cattle (73.5%). The amino acid sequences deduced from these cDNA indicate a homology with human (78.0%) and cattle (76.2%) (unpublished data). We reported that the bovine antibody developed previous study was able to detect the chicken ALS (Kim et al., 2006). For the first time, we show that Plasma ALS is present in broiler, layer and Korean native chicken by western blotting (Figure 3). This finding may provide possible future directions for ALS regulation and action on development and growth in chickens.

### CONCLUSION

A large amount of evidence in our knowledge of the somatotrophic, thyrotropic and IGF axis, primarily in mammals, suggest that GH and IGF system modulate development and growth. In many way mammals regarding these mechanisms are similar to chicken. However, it is clear that several unique differences exist. Despite an increasing understanding of the endocrine regulation on chicken growth, there are many questions remaining to be elucidated. More studies are required to identifying the role

of IGF-II and IGFBPs on development, quantifying the expression and abundance of ALS, and regulating IGF-IGFBP complexes by ALS.

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