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The Power of an Evolutionary Perspective in Studies of Endocrinology

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1. Introduction

Much of our understanding of the molecular basis of endocrinology has been the product of highly productive studies that have focused on specific molecules (e.g., hormones) and their specific immediate interacting partners. However, biomolecules are not isolated particles, but instead they are elements of highly integrated interaction networks, and specific interactions among them drive virtually all cellular functions and underlie phenotypic complexity and diversity. Many hormones, and their specific receptors and other interacting proteins, are known to be evolutionarily related, which raises intriguing questions concerning how specificity originated within these systems.

Our previous studies have illustrated that biochemical entities are developmentally and evolutionarily fluid, with capabilities to be altered both in composition and behavior. Gene birth and death are widespread phenomena in genome evolution and accounts for the great diversity of gene families involved in endocrinology. While concordance of evolutionary histories both in pattern and process of hormones, receptors and interacting proteins might be expected for integrated systems, studies have shown that the evolutionary history of receptors need not mirror that of their ligands. Simultaneous emergence, or loss, of multiple interacting partners by multiple gene duplication or gene loss is unlikely in evolution. Gene duplication is essential in the development of complex endocrinology. It is creative in producing elements that allow evolutionary tinkering and thus plays a major role in gene co-option (i.e., recruitment for novel functions) facilitating the evolution of greater biological complexity. Alternatively, if an interacting partner is lost, the retained partner may either be subsequently lost or, more interestingly, serve as raw material in evolution and become recruited into a new interaction yielding a new function. Thus, a stepwise process of elaboration through mutation and optimization ensues, adapting genes (and their encoded proteins) into the physiology of an organism.

Here we review several recent advances in our understanding of the evolution of hormone signalling pathways that illustrate the power of an evolutionary perspective. Among our

examples are the motilin and ghrelin signalling pathways where we have demonstrated that both the hormones (motilin and ghrelin) and their specific receptors descended from common ancestors through independent gene duplications. The motilin receptor originated well before the evolution of the hormone, and the motilin-motilin receptor specificity has arisen, as the result of ligand-receptor coevolution, after the hormone gene duplicated. Similarly, motilin and its specific receptor gene specifically lost on the rodent lineage followed a stepwise process. Once one of the interacting partners is lost, the retained partner may subsequently be lost, or serve as raw material in evolution and become recruited into a new function.

Given the evolutionary dynamics of the genome and the plasticity of biomolecule networks, an evolutionary perspective is necessary to understand many aspects of the molecular basis of endocrinology. An integrated evolutionary comparative strategy helps enhance our understanding of the assemblage of the complex endocrine systems, provide important clues in interaction capacity exploration, and identify the main diversification events of the endocrine systems and potential cross-talk between them through evolutionary related interacting proteins. In addition, knowledge of how elements of the endocrine systems that underlie cellular functions are evolutionarily and developmentally interact, help not only in choosing appropriate species to examine function, but also provide genetic makers to probe the emergence of specific traits and characteristics, uncovering the genetic basis that underlie the morphological and behavior changes, and thus enhance our understanding of how organisms adapt to changing environments.

2. The molecular basis of endocrine systems

Endocrinology is the branch of biology that focuses on regulatory systems involving a group of specialized chemical substances called hormones that travel though blood. New developments in endocrinology have been dominated by progress in molecular genetics. Although these investigations often relate to rare single gene disorders, they have resulted in major advances in our understanding of the cellular mechanisms of hormone action (Cegla, Tan and Bloom 2010; Hodson et al. 2010; Peter and Vallo 1998). Most endocrinology studies are medically orientated, and thus anthropocentric, with little or no comparative or evolutionary perspective, and therefore provide few insights into our comprehension of the enigmatic origin and diversification of these systems (Markov et al. 2008).

Much of our understanding of the molecular basis of endocrinology has come from highly productive studies that have focused on specific molecules and their immediate interacting partners, in fact, hormonal systems are a central part. Indeed the specificity of each hormone ligand and receptor pair is maintained in divergent species (Moyle et al. 1994), while biochemical entities are developmentally and evolutionarily fluid, with a much wider range of capabilities for alteration in both composition and behavior (Avise and Ayala 2007; Wilkins 2007). Thus intriguing questions concerning how the diversity and specificity occur within these systems remain to be answered.

Genomes are documents of life history, and their structures continually change throughout evolution. Humans represent only a leaf on the tree of life. The anthropocentrism view of evolution, where humans are the pinnacle of gradually developed complexity, is a one-sided and incorrect view (Markov et al. 2008). In the light of evolution, an approach that considers each taxa equally, adopts a comparative strategy, integrates information from diverse organisms and various scientific approaches, helps enhance our understanding of

the assemblage of the complex endocrine systems and the main events that have prompted their diversification, and yields better insight into their biological functions and potential cross-talk between them through evolutionary related interacting proteins.

3. Evolutionary mechanisms for the diversification of endocrine systems

Genomes are the entirety of organisms' hereditary information, and encode all the information necessary to give rise to biomolecular products. The structure and content of genomes do not remain static, and continually change through evolutionary time. Major evolutionary mechanisms that have been instrumental in shaping the genome include gene duplication, gene loss and evolutionary shift.

3.1 Gene duplication

As genome size increases, gene content tends to increase, although at a disproportionately lower rate in eukaryotes compared to non-eukaryotes (Gregory 2005; Hou and Lin 2009; Konstantinidis and Tiedje 2004; Lynch and Conery 2003). The gene number increases with genome size, and morphological complexity is mostly generated by expanding the sizes of gene families rather than due to a growth of the number of unique gene types, hence multicellular organisms employ large sets of similar gene products while exhibiting extraordinary biodiversity. The elements of endocrine systems often group into families (e.g., hormones and their specific receptors), whose members have diverged to various extents in regulation and function (Danks et al. 2011; Hoffmann and Opazo 2011; Irwin 2010; Kim et al. 2011; Sundström, Dreborg and Larhammar 2010).

Gene duplication is the most important mechanism for generating new genes and new biochemical processes and has facilitated the evolution of biodiversity and complexity (Li 2006; Ohno 1970). The most obvious contribution is supplying the raw genetic material for the various evolutionary forces (e.g., mutation, genetic drift and natural selection) to act upon, which lead to specialized or new gene functions (Zhang 2003). Without gene duplication, the capability and plasticity of organisms in adapting to changing environments would be severely limited. Gene duplication can also contribute to species divergence (Ting et al. 2004) along with the origin of species-specific features (Zhang et al. 2002). Duplication may involve part of gene, a single gene, part of a chromosome, an entire chromosome, or the whole genome. The first four scenarios are also known as regional duplications, because they do not result in a doubling of the entire genome. Hereinafter, the role of whole genome duplication and regional duplication will be discussed respectively.

3.1.1 Whole genome duplication

Genome duplication is often considered to be more important than regional duplication in evolution, as it allows for the duplication of the entire regulatory systems. Regional duplications, on the other hand, generally allow for part of a regulatory system to be duplicated, which may lead to imbalances that may disrupt normal function. The significance of whole genome duplication has been highlighted by the studies of invertebrate chordates and the base of vertebrate evolution (Garcia-Fernández and Holland 1994), as well as fish diversification (Dehal and Boore 2005; Jaillon et al. 2004). Genome duplication facilitated the appearance and diversification of complex features, such as the endocrine system (Holland et al. 2008). The amphioxus genome exhibits considerable

synteny with the human genome, but lacks the whole-genome duplications characteristic of vertebrates (Dehal and Boore 2005). Holland et al. (2008) examined the existence of endocrine components based on the amphioxus genome, and reasoned that ancestral chordate only possess a basic set of endocrine functions. Hereby a fully functional endocrine system must have arisen after the divergence of cephalochordate, which was driven in all probability by subsequent genome duplications.

3.1.2 Regional duplication

While whole genome duplication events are not uncommon, nevertheless they only infrequently contribute to the evolution of well-developed bisexual organisms, as they likely disrupt the mechanism of sex determination and would be quickly eliminated (Li 1997). Regional duplications make up the gap, providing new genetic material for local elaboration and optimization, and fuel the evolution of lineage-specific variability (Li 1997; Ohno 1970). Whole genome duplications and small-scale duplications have very different consequences. Selective retention of different duplicates, and enrichment of signaling proteins and transcription factors, have been observed in yeast, plants, early vertebrate and fish following whole genome duplications (Conant 2010; Gout, Duret and Kahn 2009; Huminiecki and Heldin 2010; Kassahn et al. 2009; Manning and Scheeff 2010). This indicates that the individual duplication of signaling proteins and transcriptional regulators may be deleterious, since interactions between them are relatively transient and subtle, requiring a dosage balance from the whole genome duplication to survive. It is reasonably to expect that, simultaneous duplications of ligands and downstream signaling genes are required to allow the expansion of the complex endocrine systems. As it is, only part of the regulatory system has been duplicated in regional duplication, then, what are the evolutionary consequences of such an imbalanced outcome?

3.2 Gene loss

Studies on genome evolution have focused on the creation of new genes, including changes in regulatory mechanisms, and often neglect the role of selective gene loss in shaping these genomes. Gene loss or pseudogenization is a widespread phenomenon in genome evolution (Wang, Grus and Zhang 2006). The differential fixation of mutational gene loss after genome duplication illustrates the power of these types of events (Semyonov et al. 2008; van Hoek and Hogeweg 2009). Within gene families gene turnover, caused by differential gene gain and loss, leads to diverse patterns of gene distributions on different lineages, and contributes significantly to the evolution of biodiversity and may be the basis for reproductive isolation and speciation in geographically isolated populations (Gagneux and Varki 2001; Gout, Duret and Kahn 2009; Hahn, Demuth and Han 2007; Kettler et al. 2007; Powell et al. 2008). Sometimes, the ubiquitous, and near-stochastic, gene loss process can lead to the loss of single copy genes. By taking advantages of the availability of large amounts of vertebrate genomic information, it has been shown that many important human endocrine genes have been found to be missing or inactivated in other vertebrates, and vice versa (He et al. 2010; Irwin 2010; Pitel et al. 2010). In the same way, evolutionary comparisons among different taxa can help identify novel elements of endocrine systems that are not possessed by model animals. Endocrine entities are not isolated particles, but are elements of highly integrated interaction networks, and play their role through specific interactions (Carroll, Bridgham and Thornton 2008). As a random process, the simultaneous

loss of multiple interacting partners is unlikely, despite the intimate association between them. Gene loss, a dramatic genetic event, leads to the immediate loss of specific interactions, and probably affects interaction turnover as greatly as gene duplication. If a signaling protein is lost, then what are the evolutionary consequences for the retained partners?

3.3 Evolutionary shift

Genes are not only duplicated and lost, there are many genes which have been conserved and are unambiguous orthologues in a wide variety of taxonomic species, but evolutionary shifts occur frequently and orthologues genes can have distinct functions in different taxa (Macqueen et al. 2010; Zhou et al. 2008). Species adapt to diverse ecosystems and environments, and have differing genetic backgrounds. As selective constraints vary, it impacts the pattern of gene evolution, and changes in selection can yield changes in function (Irwin 2001). In some cases, positive selection appears to underlie the evolutionary shift (Wallis 2001; Liu et al. 2001); while in others, inefficient purifying selection and increased genetic drift, associated with a reduction in effective population size, are the cause (Macqueen et al. 2010).

The genetic network of the endocrine systems are developmentally and evolutionarily fictile, the elemental composition is prone to be altered via gene gain and loss, and its physiological properties frequently change through mutations in endocrine gene coding sequences and/or regulatory systems, and turnover of interacting biomolecules. Using a comparative strategy, integrating information on species phylogenetic relationships, gene evolutionary history, gene sequences and functional properties such as expression, interaction and physiological data, should enhance our understanding of how they evolved and yield better insight into their biological functions. The large amounts of accumulating genetic information is a powerful resource for addressing these questions.

4. Case studies for evolutionary endocrinology: Lessons from the motilin/ghrelin hormone family and their receptors

4.1 Gene duplication plays a major role in gene co-option

4.1.1 Ghrelin and motilin

Ghrelin and motilin represent a novel gastrointestinal hormone family in mammals (Inui 2001). Not only are ghrelin and motilin structurally related, but, the sequence and overall structure of their precursor genes show considerable similarity (Fig. 1).

Ghrelin is derived by posttranslational cleavage from its precursor preproghrelin (GHRL), and is a circulating peptide hormone that is secreted mainly by the stomach and acts upon the hypothalamus and hindbrain (Nakazato et al. 2001; Kojima and Kangawa 2005). Growth hormone secretagogue receptor (GHSR) is the specific receptor for ghrelin and a G protein-coupled receptor, and upon stimulation releases growth hormone (GH) from the pituitary (Howard et al. 1996; Kojima et al. 1999; Sun, Ahmed and Smith 2003). Evidence from mammals suggests that ghrelin also acts to stimulate gastric motility, increase appetite and food intake, and induce a positive energy balance leading to body weight gain (Murray et al. 2003; Peeters 2005). Prepromotilin (MLN) is posttranslationaly processed to yield a secreted peptide that is then cleaved at a paired basic amino acid site and gives rise to motilin (Poitras 1993). Motilin primarily acts to increase gastrointestinal motility by activating neural pathways or via the direct stimulation of smooth muscles. In human and dog it has been suggested that motilin has a physiological role in the regulation of a motor pattern

typical for the fasted state (Poitras 1993). It is of interest to note that motilin also has a weak GH-releasing effect (Samson et al. 1984). GPR38, an orphan G protein coupled receptor, was identified as the motilin receptor, MLNR, through a remarkable process of reverse pharmacology (Feighner et al 1999). GHSR and MLNR, whose sequences are very similar, are members of the β-group of rhodopsin-like receptor family (Holst et al. 2004).
Despite the very close resemblance of the hormones and receptors, to date there is no evidence for any cross-reactivity between the ligands, which corresponds to the fact that the pharmacophore of the peptides are quite different (Peeters 2005). Octanoylation of serine^3 is a unique and crucially important feature of ghrelin and studies have demonstrated that without the octanoyl group the potency of GHRL is dramatically decreased (Peeters 2005; Kaiya et al. 2001).

4.1.2 Evolution of the motilin/ghrelin hormone gene family

Genes for ghrelin have been cloned from a number of vertebrate species. Using bioinformatic methods, we have identified additional ghrelin gene sequences from diverse mammalian species and a frog *Xenopus tropicalis* (Table 1). Motilin genes have only been identified and characterized in mammals and birds, even after the use of bioinformatic approaches (Table 2). Ghrelin and motilin genes are both single copy genes in all of the species studied, and reside in conserved gene neighborhoods respectively, strongly supporting their orthology. The amino acid sequences of ghrelin are well conserved among species, especially in the N terminal region, and the same principle holds for motilin (Table 1-2). Interestingly, when the comparative genomic analysis was conducted between human and other vertebrates (chicken, *X. tropicalis*, medaka, tetraodon, and zebrafish) aimed at the GHRL and MLN neighborhood regions, it was revealed that homologs of the human GHRL and MLN flanking genes, which are located on different chromosomes in amniotes, were found to reside on the same chromosome near the GHRL locus in medaka, tetraodon, zebrafish, and *X. tropicalis*. This observation suggests that there was a duplication of the GHRL gene yielding MLN on the amniote lineage however there was no overlap in the genomic neighborhoods for GHRL and MLN. We could not identify any sequences similar to ghrelin and/or motilin genes in the recently released lamprey and deuterostome draft genomes. GHRL sequences from fish and amphibians posses only a single putative endoproteinase recognition site C-terminal to the signal peptidase cleavage site, thus can produce only a single posttranslational-processed peptide, ghrelin. In contrast, GHRL of amniotes (reptiles, birds, and mammals) possess three putative endoproteinase recognition sites, potentially giving rise to a second posttranslational-processed peptide, a 24-residue ghrelin-associated peptide (Fig. 1). The second peptide has recently been identified to be obestatin in mammals (Zhang et al. 2005). All MLNs, which are only found in reptiles, birds and mammals, possess three putative endoproteinase recognition sites, thus potentially give rise to two posttranslational-processed peptides, motilin and a 17-residue peptide in a position homologous to obestatin (Fig 1). Phylogenetic analysis revealed that bullfrog GHRL groups with amniote MLN rather than amnitote GHRL, although the bootstrap support for this conclusion is low (Fig. 2).
Based on the distribution of GHRL and MLN genes in the species studied, comparative genomics analysis between human and other vertebrates, and endoproteinase cleavage sites distribution in GHRL/MLN genes, we surmise that MLN was generated by a gene duplication on the early amniote lineage as illustrated in figure 2 (He et al. 2011). Other potential evolutionary scenarios (e.g., duplication prior to the fish-tetrapod divergence) require a larger number of gene deletion events along with parallel gain or loss of endopeptidease cleavage sites, and thus are less parsimonious.

Species	Ghrelin sequence	Obestatin homolog sequence
Homo sapiens	GSSFLSPEHQRVQQRKESKKPP AKLQP	FNAPFDVGIKLSGVQYQQHS QALG
Pan troglodytes	GSSFLSPEHQRVQQRKESKKPP AKLQP	FNAPFDVGIKLSGVQYQQHS QALG
Pongo pygmaeus	GSSFLSPEHQRVQQRKESKKPP AKLQP	FNAPFDVGIKLSGVQYQQHS QALG
Hylobates lar	GSSFLSPEHQRVQQRKESKKPP AKLQP	FNAPFDVGIKLSGVQYQQHS QALG
Macaca fuscata	GSSFLSPEHQRAQQRKESKKPP AKLQP	FNAPFDVGIKLSGVQYQQHS QALG
Papio hamadryas	GSSFLSPEHQRAQQRKESKKPP AKLQP	FNAPFDVGIKLSGVQYQQHS QALG
Saimiri sciureus	GSSFLSPEHQRIQQRKESKKPPA KLQP	FNAPFDVGIKLSGVQYQQHS QALG
Macaca mulatta	GSSFLSPEHQRAQQRKESKKPP AKLQP	FNAPFDVGIKLSGVQYQQHS QALG
Otolemur garnettii	GSSFLSPDHQKIQQRKESKKPPA KLQP	FNSPLDVGIKLSGAQYQQHS QALG
Cebus paella	GSSFLSPEHQRMQQRKESKKPP AKLQS	FNVPFDVGIKLSGVQYQQHS QALG
Aotus trivirgatus	GSSFLSPEHQRIQQRKESKKPPA KLQP	FNAPFDVGIKLSGIQYQQHSQ ALG
Mesocricetus auratus	GSSFLSPEHQKAQQRKESKKPQ AKLQP	FNAPFDVGIKLSGAQYQQHG RALG
Mus musculus	GSSFLSPEHQKAQQRKESKKPP AKLQP	FNAPFDVGIKLSGAQYQQHG RALG
Rattus norvegicus	GSSFLSPEHQKAQQRKESKKPP AKLQP	FNAPFDVGIKLSGAQYQQHG RALG
Meriones unguiculatus	GSSFLSPEHQKTQQRKESKKPP AKLQP	FNAPFDVGIKLSGAQYQQHG RALG
Oryctolagus cuniculus	GSSFLSPEHQKAQQRKDAKKPP ARLQP	
Felis catus	GSSFLSPEHQKVQQRKESKKPP AKLQP	FNAPFDVGIKLSGAQYHQHG QALG
Canis familiaris	GSSFLSPEHQKLQQRKESKKPP AKLQP	FNAPFDVGIKLSGPQYHQHG QALG
Equus caballus	GSSFLSPEHHKVQHRKESKKPP AKLKP	FNAPFDVGIKLSGAQYHQHS QALG
Rangifer tarandus	GSSFLSPEHQKLQRKEPKKPSGR LKP	FNAPFDIGIKLSGAQSLQHGQ TLG
Capra hircus	GSSFLSPEHQKLQRKEPKKPSGR LKP	FNAPFNIGIKLSGAQSLQHGQ TLG
Ovis aries	GSSFLSPEHQKLQRKEPKKPSGR LKP	FNAPFNIGIKLSGAQSLQHGQ TLG
Bos taurus	GSSFLSPEHQKLQRKEAKKPSG	FNAPFNIGIKLAGAQSLQHG

Species	Ghrelin sequence	Obestatin homolog sequence
	RLKP	QTLG
Bubalus bubalis	GSSFLSPEHQKLQRKEPKKPSGRLKP	FNAPFNIGIKLSGAQSLQHGQTLG
Ailuropoda melanoleuca	GSSFLSPEHQKVQRKESKKPPAKLQP	FNAPFDVGIKLSGAQYQEHGQALG
Sus scrofa	GSSFLSPEHQKVQQRKESKKPAAKLKP	FNAPCDVGIKLSGAQSDQHGQPLG
Kogia breviceps	GSSFLSPEHQKLQRKEAKKPSGRLKP	
Myotis lucifugus	GSSFLSPEHQKAQQRKESKKPPAKLQP	FNAPFDVGIKLSGAQSHWHGQALG
Erinaceus europaeus	GSSFLSPEHQKGQQRKEPKKPPGKVQP	FSAPFDVGLRLSGAQYEQHGEALR
Dasypus novemcinctus	GSSFLSPEHQKTQLRKEFKKPATKLQP	FNAPFDVGIKLSGAQYQQHGRSLG
Echinops telfairi	GSSFLSPGHPKVQPQRKESKTPAGKLQA	FNVPFDIGIKVSVAQYGEHGRALD
Loxodonta africana	GSSFLSPKNQKLQQRKESKKPPAKLQP	
Monodelphis domestica	GSSFLSPEHPKTQRKETKKPSVKLQP	FNAPFDIGIKVAEAQYQQYGHALE
Gallus gallus	GSSFLSPTYKNIQQQKDTRKPTARLH	FNVPFEIGVKITEREYQEYGQALE
Meleagris gallopavo	GSSFLSPAYKNIQQQKDTRKPTARLHP	FNVPFEIGVKITEREYQEYGQALE
Anas platyrhynchos	GSSFLSPEFKKIQQQNDPTKTTAKIH	FHVPFEIGVKITEEEYQEYGQTLE
Anser sp.	GSSFLSPEFKKIQQQNDPAKATAKIH	FNVPFEIGVKITEEEYQEYGQTLE
Dromaius novaehollandiae	GSSFLSPDYKKIQQRKDPRKPTTKLH	FNVPFEIGVKITEEQYQEYGQMLE
Trachemys scripta elegans	GSSFLSPEYQNTQQRKDPKKHTKLN	LNVPFEIGVKITEDQYQEYGQVLE
Rana catesbeiana	GLTFLSPADMQKIAERQSQNKLRHGNMN	
Rana esculenta	GLTFLSPADMRKIAERQSQNKLRHGNMN	
Danio rerio	GTSFLSPTQKPQGRRPPRVG	
Carassius auratus	GTSFLSPAQKPQGRRPPRMG	
Ictalurus punctatus	GSSFLSPTQKPQNRGDRKPPRVG	
Oreochromis mossambicus	GSSFLSPSQKPQNKVKSSRIG	

Species	Ghrelin sequence	Obestatin homolog sequence
Oreochromis niloticus	GSSFLSPSQKPQNKVKSSRIG	
Oncorhynchus mykiss	GSSFLSPSQKPQGKGKPPRVG	
Acanthopagrus schlegelii	GSSFLSPSQKPQNRGKSSRVG	
Anguilla japonica	GSSFLSPSQRPQGKDKKPPRVG	

Table 1. Bioactive peptide sequences from diverse vertebrata ghrelin gene.

Species	Motilin sequence
Homo sapiens	FVPIFTYGELQRMQEKERNKGQ
Pan troglodytes	FVPIFTYGELQRMQEKERNKGQ
Macaca mulatta	FVPIFTYGELQRMQEKERSKGQ
Cavia porcellus	FVPIFTYSELRRTQEREQNKRL
Oryctolagus cuniculus	FVPIFTYSELQRMQERERNRGH
Felis catus	FVPIFTHSELQRIREKERNKGQ
Canis familiaris	FVPIFTHSELQKIREKERNKGQ
Ovis aries	FVPIFTYGEVQRMQEKERYKGQ
Bos taurus	FVPIFTYGEVRRMQEKERYKGQ
Sus scrofa	FVPSFTYGELQRMQEKERNKGQ
Equus caballus	FVPIFTYSELQRMQEKERNRGQ
Myotis lucifugus	FVPIFTHSELQRMQEKERNKEQ
Dasypus novemcinctus	FVPIFTYSELQRMQEKEWNKGQ
Loxodonta africana	FVPIFTYSEIRRMQERERNNGQ
Monodelphis domestica	FVPIFTYSDVQRMQEKERNKGQ
Ornithorhynchus anatinus	FIPIFTHSDVQRMQERERNKGQ
Gallus gallus	FVPFFTQSDIQKMQEKERNKGQ

Table 2. Bioactive peptide sequences from diverse vertebrata motlin gene.

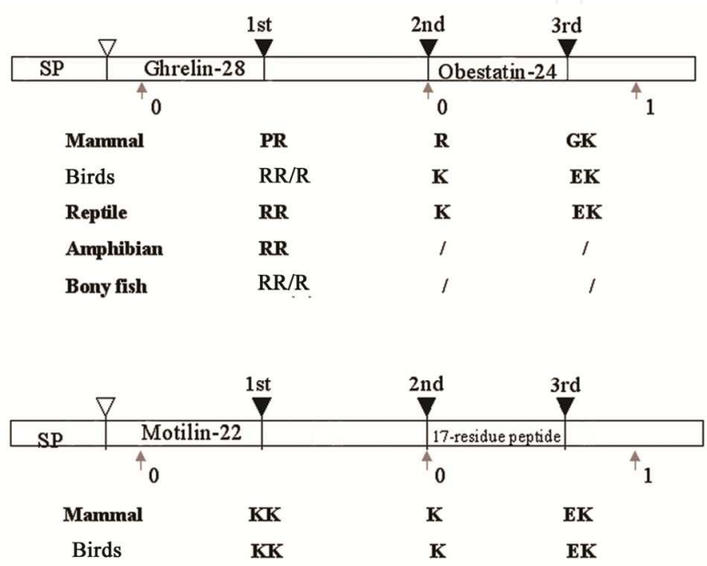

Fig. 1. Schematic representation of ghrelin and motilin preproproteins. The preproproteins of ghrelin and motilin are represented by boxes divided into protein domains, proportional to their length. The open and filled triangles indicate the locations of cleavage sites used by signal peptidase and proprotein convertase, respectively. The sequences of the putative endoproteinase cleavage sites of various vertebrate classes are shown bellow. Alternative processing sites in birds and bony fish are indicated, "↑" denotes intron position with intron phase shown beside the arrow. SP, signal peptide. "/", lack of putative endoproteinase recognition sites.

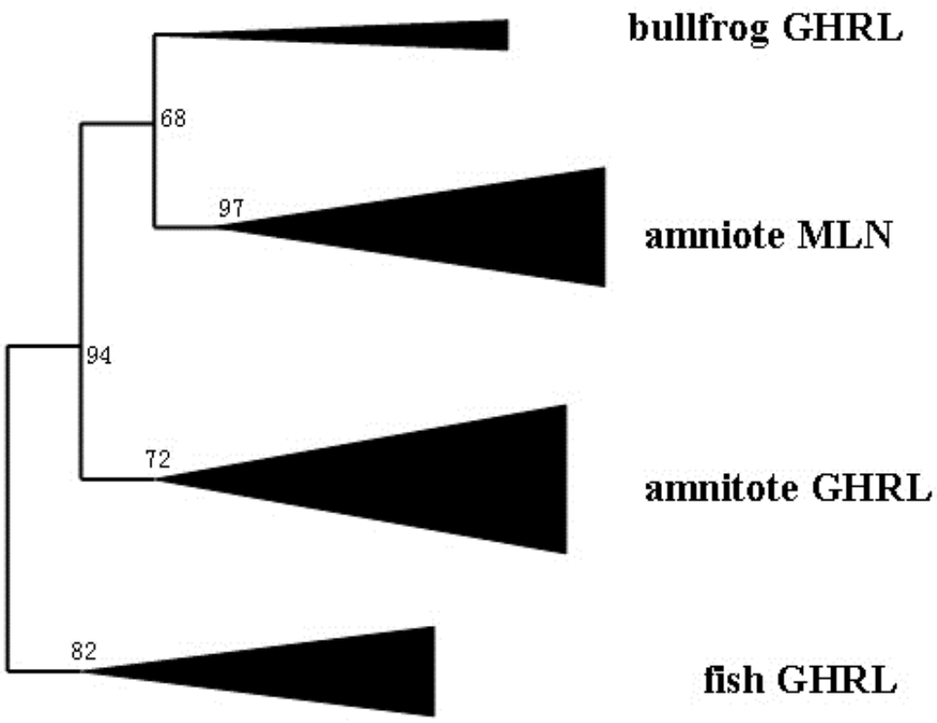

Fig. 2. Schematic representation of the motilin/ghrelin gene family phylogenetic relationships. Bootstrap percentages are shown on interior branches. GHRL, preproghrelin. MLN, prepromotilin.

4.1.3 Evolution of ghrelin and motilin receptors

Only a small number of Ghrelin and motilin receptor genes are known and most of these are from mammals, with ortholog from only two species of fish having previously being characterized (Palyha et al. 2000; Chan and Cheng 2004). Our bioinformatic searches of diverse vertebrate genomes resulted in the identification of a great number of potential receptors. The orthology of the different receptors was established using analysis of synteny of the genes. In combination with phylogenetic reconstruction, the monophyly of each receptor type was established, and no more than one copy of each type of receptor was identified in any of the studied species. GHSR and MLNR are more closely related to each other than they are to any other characterized receptor, and the gene duplication that generated them happened more than 450 million years ago, before the divergence of ray-finned fish and tetrapods (He et al. 2011). Through comparative and evolutionary analyses, we found a new type of receptor in fish, which does not have an ortholog in any non-fish vertebrate. The function of this new receptor is unknown. The sequence of this new receptor has some peculiarities, such as possessing long extracellular loops 2 and 3, which are about 100 residues longer than the analogous loops in GHSR and MLNR (He et al. 2011). Residues at both ends of these loops have been shown to be functionally important for hormone binding and action in homologous receptors; however, the function of these residues in the loops of these novel receptors is not clear (Matsuura, Dong and Miller 2002).

Studies have shown that the GHSR orthologs in fish can be activated by growth hormone secretagogues (GHSs), while MLNR orthologs in fish failed to be activated by GHSs or mammalian motilin (Palyha et al. 2000). The identification of the ancient binding state of MLNR prior to the emergence of motilin has proven challenging, however it is reasonable to speculate that GHSR and MLNR experienced functional diversification shortly after their duplication, and the ancient MLNR did not have either ghrelin or motilin binding properties. Evolutionary studies suggest MLNR experienced an episode of rapid evolution on the branch leading to amniotes, which was driven by positive selection, and accumulated amino acid changes in ligand binding cleft. This time period of rapid evolution coincides with the date of the GHRL/ MLN gene duplication event, thus it is reasonable to speculate, that the burst of rapid evolution in MLNR was a consequence of coevolution with its new ligand, and that motilin binding specificity of MLNR only evolved as a result of ligand-receptor coevolution after the motilin gene diverged from the ghrelin gene on the amniote lineage. In contrast, GHSR has evolved under a constant selective constraint throughout vertebrates, with the ghrelin/GHSR system being maintained and functionally conserved from fish to mammals (He et al. 2011).

4.1.4 Gene duplication and gene co-option

The motilin/ghrelin hormone and their receptors were produced by independent duplication events that occurred at different points in time. The discordance of the evolutionary histories for the hormones and receptors indicate that the intimate interacting partners of an endocrine system can be produced by individual duplications, the composition and functions of each part of the endocrine network do not remain static, and that parts of a system can be co-opted for novelties, and that these processes often involve gene duplication and subsequent divergence. Structural and evolutionary relatedness allows promiscuous interaction properties, which can serve as the starting point for accommodation. Divergence of function in different species is accomplished by hormone/receptor coevolution to improve binding affinity and/or specificity. A major role

for gene co-option, involving gene duplication and divergence, should be recognized that creates potential elements which selection can act upon within a biological network to evolve new functions (He et al. 2011; True and Carroll 2002). The growth of gene families allows for more flexible gene expression and/or the evolution of new biochemical specificities (Rubenstein 1990; Sharman and Holland 1996), thus facilitating the evolution of greater biological complexity (Duboule and Wilkins1998).

4.2 Loss of the motilin and its specific receptor genes in rodents

The evolution of motilin and its specific receptor in rodents provides an illustration of the consequences of gene loss. Motilin is a 22-amino acid peptide synthesized by endocrine cells of the duodeno-jejunal mucosa and has a profound stimulatory effect on gastrointestinal contractility (Poitras and Peeters 2008), indicating that motilin and its specific receptor serve as potent active prokinetic drug target candidates. However, the clinical development of potential therapies is limited as both the mouse and rat, the most frequently used laboratory animals, are natural knockouts for the motilin and its specific receptor, that is these animal lack these genes and functional targets (He et al. 2010). These observations raise a number of intriguing questions – how can these animals survive without motilin? How were the genes lost? Did any other endocrine system compensate? What does this mean for our understanding of the human hormones? While we can't answer all of these questions, our studies revealed that the motilin receptor was pseudogenized specifically on the rodent lineage, while the motilin gene exhibited diverse evolutionary consequences in different rodent species (He et al. 2010). Once an interacting partner is lost, retained partners may be lost, as demonstrated by the independent loss of MLN in mice, rats and in the guinea pig, or serve as raw material in evolution, as suggested by the retention of MLN in the kangaroo rat. Genomic sequence information suggest, that in the the monophyletic Dipodomyinae subfamily, the MLN gene is intact and is under sustained evolutionary constraint, suggesting it has been recruited into a novel function, a function distinct from traditional motilin signaling (our unpublished observations). Intriguingly, studies have suggested that, after the break down of the MLN signaling pathway, the ghrelin signaling pathway was recruited to compensate for this loss in the rat (Dass et al. 2003; Depoortere et al. 2003). Given the ubiquity and its stochastic nature, the simultaneous loss of a hormone and its specific receptor is unlikely. As a dramatic genetic change, a gene loss leads to an immediate loss of specific interactions. The functional redundancy among gene family members could allow a compromise for the deleterious gene loss. Existing genes can be modified, or recruited, into new interactions that yield new functions through mutation and optimization (Jacob 1977; Khersonsky, Roodveldt and Tawfik 2006; Tokuriki and Tawfik 2009). Motilin is not a unique case. As similar events have occurred to leptin, an important adipose derived hormone (Brennan and Mantzoros 2006; Zhang et al. 1994), which does not exist in the chicken, and likely other birds, while a functional leptin receptor has conserved in these species (Horev et al. 2000; Ohkubo, Tanaka and Nakashima 2000; Pitel et al. 2010). It is possible that the lineage specific losses of motilin and leptin during evolution contributed to the evolution of novel metabolic regulatory mechanisms in these species.

4.3 Evolutionary shifts in existing genes

The proglucagon gene illustrates some of these issues. The vertebrate proglucagon gene encodes three glucagonlike sequences (glucagon, glucagon-like peptide-1 [GLP-1], and glucagon-like peptide-2 [GLP-2]) that play distinct roles in mammalian metabolic regulation

(Drucker 2001; Drucker 2002; Jiang and Zhang 2003; Kieffer and Habener 1999). Glucagon, produced by the A cells of the pancreatic islets, counteracts insulin's effect on blood glucose level depression (Jiang and Zhang 2003). GLP-1 functions as an incretin hormone in mammals, potentiating insulin release, and thus regulating glucose metabolism (Drucker 2001, 2002). In contrast, glucagon and GLP-1 have similar physiological functions in fish, and resemble that of mammalian glucagon (Duguay and Mommsen 1994; Plisetskaya and Mommsen 1996). The receptors for glucagon, GLP-1, and GLP-2 have emerged before the divergence of fish and mammals; however, the GLP-1 class of receptors has specifically been lost in fish, and accordingly the incretin action of GLP-1. A fish specific duplication produced a second glucagon receptor-like gene on the ancestral fish lineage. The new glucagon receptor-like gene shifted its binding specificity from glucagon to GLP-1 ensues, meanwhile maintained the ancestral downstream signaling. Thus through receptor loss and gain, existing hormone was recruited into new roles, and undoubtedly enabled evolutionary divergence (Irwin and Wong 2005).

While ghrelin and its specific receptor (GHSR) genes has been maintained and functionally conserved from fish to mammals, there are some significant differences in the function of the ghrelin/GHSR system in birds compared to other vertebrates (Richards 2010). Some of the actions of ghrelin are conserved in birds (e.g., GH release), while others, such as the effect of ghrelin on food intake, are opposite to those found in mammals and other vertebrate species (Hiroyuki et al. 2007; Kaiya et al. 2009; Kaiya et al. 2008). Besides ghrelin, the ghrelin gene has the potential to encode another peptide hormone——obstatin (Zhang et al. 2005). We observed episodic evolution for both the ghrelin and motilin genes during primitive placental mammal evolution, the period when a functional obestatin hormone might have originated (He, Irwin and Zhang 2010). It is possible that some of the lineage-specific physiological adaptations are due to the episodic evolution of the motilin and ghrelin genes.

Gene duplication, pseudonization, and the gain and loss of interactions through mutations in existing genes are major evolutionary processes shaping the specific interaction among biomolecules (Berg, Lässig and Wagner 2004; Wagner 2001; Wagner 2003; He et al. 2010). Thus, once a mutation arises, a stepwise process of elaboration and optimization ensues, which gradually integrates and orders mutations into a coherent pattern. Given the evolutionary dynamics of the genome and the plasticity of biomolecular networks, an evolutionary perspective is necessary to understand many aspects of the molecular basis of endocrinology.

5. Conclusion

Biological evolution is the process of generating biodiversity. Different phenotype corresponds to a given genomic control. New genes, new interactions, and new biochemical processes are essential for the molecular basis of the evolution of biodiversity and complexity. Genetic networks of endocrine systems are developmentally and evolutionarily fictile, elemental compositions within them are prone to be altered through gene gain and loss, and its physiological properties frequently change with mutations in gene coding sequences and/or regulatory systems, and turnover of interacting biomolecules.

The endocrine system consists of several glands in different parts of the body, which secrete hormones directly into the blood. Hormones usually have many different functions and

modes of action; one hormone may play roles in different target organs, and conversely, target organs are affected by more than one hormone. Although quite irregular, there are still some formulas that can be followed. Structural and evolutionary relatedness generate promiscuous interaction properties, and provide important clues to interaction capacity exploration. Tracing the origin and studying the molecular evolution of endocrine systems should help us comprehend the main events that have prompted the diversification of these systems. In the light of evolution, through a comparative strategy, integrating information from diverse species helps to enhance our understanding of the assemblage of complex endocrine systems, identifying novel components of endocrine systems, and potential cross-talk between them through evolutionarily related interacting proteins. In addition, knowledge of how elements that underlie cellular functions are evolutionarily and developmentally interact, not only helps in choosing appropriate species to examine function, but also provide genetic makers to probe the evolution of specific traits and characteristics, disclosing the genetic basis that underlie the morphological and behavior changes, and thus helping enhance our understanding of how changing environments led to biochemical adjustments.

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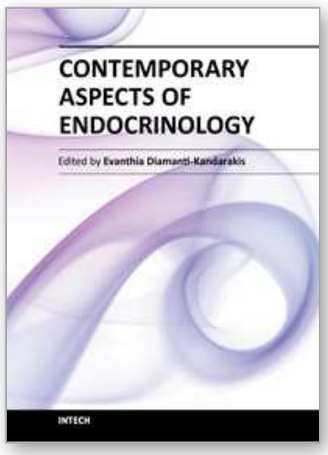

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This book aims to provide readers with a general as well as an advanced overview of the key trends in endocrine disorders. While covering a variety of topics ranging from thyroid carcinogenesis and pituitary adenomas to adrenal tumors and metabolic bone disease, this book also focuses on more specific issues not yet fully elucidated (e.g. the molecular pathways involved in thyrotropin beta gene regulation or monogenic phosphate balance disorders). Readers of different fields and background will have the opportunity to update their knowledge and more importantly to clarify areas of uncertainty and controversies in several topics of endocrine disorders.

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