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Profile of Galanin in Embryonic Stem Cells and Tissues

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1. Introduction

In the preimplantation mammalian embryo, cells of the inner cell mass can differentiate into any cell type present in the more mature embryo. As of 1981, in mice and 1998 in humans, it has been recognized that embryonic stem cells (ESCs) with a prolonged proliferative capacity can be derived from the inner cell mass in vitro (Evans and Kaufman 1981; Thomson, Itskovitz-Eldor et al. 1998). ESCs are pluripotent cells that can contribute to all tissues in vivo and to the three primary germ layers as well as extraembryonic tissues in vitro. Because pluripotency is maintained in these cells even after prolonged periods of culture, human ESCs have great therapeutic potential for tissue regeneration. Indeed, embryonic and adult stem cells (SCs) hold great promise for regenerative medicine, tissue repair, and gene therapy. Careful molecular characterization of embryonic pluripotency should help to optimize and scale up the in vitro production of ESCs for clinical applications.

The mechanisms regulating self-renewal and cell fate decisions in mammalian stem cells are poorly understood. As compared with differentiated cell types, stem cells express a significantly higher number of genes (represented by expressed sequence tags) of unknown function. The properties that distinguish stem cells from other cells are largely unknown, and the identification of signals that regulate stem cell differentiation remains fundamental to our understanding of cellular diversity.

Embryonic and adult stem cells have many similarities at the transcriptional level. The overlapping set of expressed gene products represents a molecular signature of stem cells (Bhattacharya, Miura et al. 2004; Assou, Le Carrour et al. 2007). A list of human and mouse genes involved in stemness has been generated (Assou, Le Carrour et al. 2007) and includes 92 stemness genes known to be expressed in mouse or human ESCs, e.g., OCT3/4, NANOG, Cripto/TDGFI, Cx43 and Galanin (Richards, Tan et al. 2004). Work in the field of embryogenesis has also contributed to our understanding of the function of these pluripotency-associated genes. The four most significantly overexpressed genes in undifferentiated embryonic tissues are Galanin, POU5FI, NANOG and DPPA4 (Zeng, Miura et al. 2004). In most studies, galanin has been highlighted as the most abundant transcript in ES culture as well as human and rodent embryonic tissues (Anisimov, Tarasov et al. 2002; Zeng, Miura et al. 2004). Both galanin and galanin receptors are expressed in ES cells, indicating a potential functional role for this protein (Tarasov, Tarasova et al. 2002). This chapter will be devoted to a description of the galanin expression profiles in embryonic tissues and stem cells as well as its possible functional role.

2. Galanin

Galanin was first identified from porcine intestinal extracts in 1978 by Professor Viktor Mutt and colleagues at the Karolinska Institute, Sweden, using a chemical assay technique that detects peptides according to their C-terminal alanine amide structures. Galanin is so-called because it contains an N-terminal glycine residue and a C-terminal alanine (Hokfelt and Tatemoto 2008). The structure of galanin was determined in 1983 by the same team (Tatemoto, Rokaeus et al. 1983), and galanin cDNA was first cloned from a rat anterior pituitary library in 1987 (Vrontakis, Peden et al. 1987). Galanin is a biologically active neuropeptide that is widely distributed in the central and peripheral nervous systems and the endocrine system. The N-terminus of galanin is highly conserved between species (almost 90% among vertebrates, with the first 15 amino acids being identical, indicating the likely importance of this molecule (Vrontakis 2002). Consistent with this sequence conservation, the first 15 amino acids of galanin are sufficient for agonistic receptor binding. Galanin is proteolytically processed from a 124-amino acid precursor peptide, preprogalanin, along with a 59- or 60-amino acid peptide known as galanin message associate peptide (GMAP) (Rokaeus and Brownstein 1986; Vrontakis, Peden et al. 1987; Evans and Shine 1991). Preprogalanin is encoded by a single-copy gene organized into 6 small exons (fig.1) spanning about 6 kb of genomic DNA (Kofler, Liu et al. 1996). The intron:exon organization of the galanin gene is conserved in all species studied thus far (Vrontakis 2002). Transcriptional studies of the galanin gene in multiple species concluded that the tissue-specific expression of this gene is achieved by enhancers as well as silencer
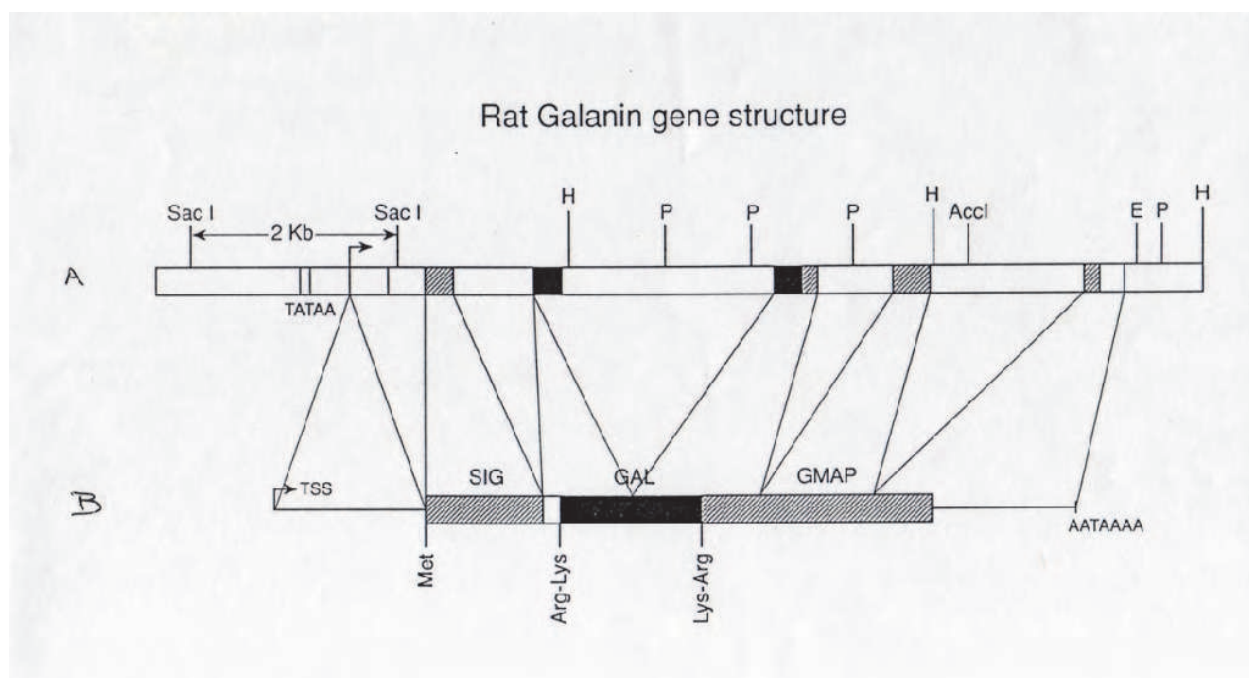

Fig. 1. Organization of the rat preprogalanin gene. A: Schematic representation of the rat preprogalanin gene. B: the position of the six exons with respect to the rat preprogalanin cDNA are shown. Abbreviations are as follows: ATG, translation initiation site; AATAAA, (Lang, Gundlach et al. 2007) the poly (A); TATA,TATA box;TSS, transcription start site; SIG, signal peptide; GAL, galanin; GAMP, galanin message associated peptide (Maria Vrontakis and Hong Zhang unpublished data)

sequences, which restrict expression to the appropriate cell type (Kofler, Evans et al. 1995; Corness, Burbach et al. 1997; Jiang, Spyrou et al. 1998; Rokaeus and Waschek 1998). We have sequence the 5' flanking region of the rat galanin gene (Zhang, 1998) and have shown that the rat galanin promoter region contains some consensus sequences for known transcription factors. Up streamed of the modified TATA box, there is a conserved half-element (TGACG) for the protein CREB, which typically mediates gene expression by binding to the cyclic AMP response element (CRE). In the rat galanin promoter region, there are also several AP-1 binding sequences for the Jun/Fos protein families. Upstream of the CREB binding site there is a c-Ets element for the Ets factors. Furthermore, both negative and positive regulatory elements exist in the rat galanin gene. The negative regulatory elements appeared to be tissue specific since they are located differently in the different tissues. These negative transcription sites in the galanin promoter might be of importance for down regulating the gene during development.

The functional role of galanin remains largely unknown, as is the case for most other neuropeptides; however, Galanin has been implicated in many biologically diverse functions, including nociception, waking and sleep regulation, cognition, feeding, regulation of mood and regulation of blood pressure. It also has roles in development and can act as a trophic factor. Galanin has been linked to a number of diseases, including Alzheimer's disease, epilepsy, depression and eating disorders. Galanin appears to have neuroprotective activity, as its biosynthesis is increased 10- to 100-fold upon axotomy in the peripheral nervous system (whereas most neuropeptides are induced only 1.5- to 2-fold) or when seizure activity occurs in the brain. It may also promote neurogenesis (Mitsukawa, Lu et al. 2008). Galanin frequently co-localizes with classical neurotransmitters such as acetylcholine, serotonin and norepinephrine as well as with other neuromodulators such as Neuropeptide Y, Substance P and Vasoactive peptide (Lang, Gundlach et al. 2007). Expression of galanin at the mRNA and peptide levels is elevated following estrogen administration, neuronal activation, denervation and/or nerve injury as well as during development. The wide spectrum of galanin's activities indicates that galanin is an important messenger for intercellular communication within the nervous system and the neuroendocrine axis.

Galanin acts at specific membrane receptors to exert its effects. To date, three human and rodent galanin receptor subtypes have been cloned, namely, GalR1, GalR2 and GalR3 (Branchek, Smith et al. 2000). High conservation between species exists among receptors of a given subtype but not between subtypes in an individual species (Howard, Tan et al. 1997; Iismaa, Fathi et al. 1998; Kolakowski, O'Neill et al. 1998). All three galanin receptor subtypes are members of the G protein-coupled receptor superfamily, but the subtypes show substantial differences in their functional coupling and subsequent signaling activities, contributing to the diversity of the possible physiological effects of galanin (Fig. 2). GalR1, the most abundant receptor subtype in adult tissues, is associated with the Gi family, which mediates the inhibition of cAMP synthesis by adenylate cyclase. Furthermore, it opens G-protein-regulated inwardly rectifying potassium channels and stimulates mitogen-activated protein kinase (MAPK) activity. GalR2 acts through Gq/11 to regulate phospholipase C-mediated events. GalR3 couples to Gi/Go and mediates the opening of G protein-coupled inwardly rectifying potassium channels (Lang, Gundlach et al. 2007). Since the three galanin receptors exhibit distinct but overlapping patterns of expression in the central and peripheral nervous systems, a variety of ligands have been developed in an effort to elucidate the specific roles of each receptor (Langel and Bartfai 1998; Pooga, Jureus et al. 1998; Lu, Lundstrom et al. 2005). Galanin agonists have been shown to have therapeutic

applications in the treatment of chronic pain. Conversely, galanin antagonists have therapeutic potential for the treatment of Alzheimer's disease, depression, and eating disorders.
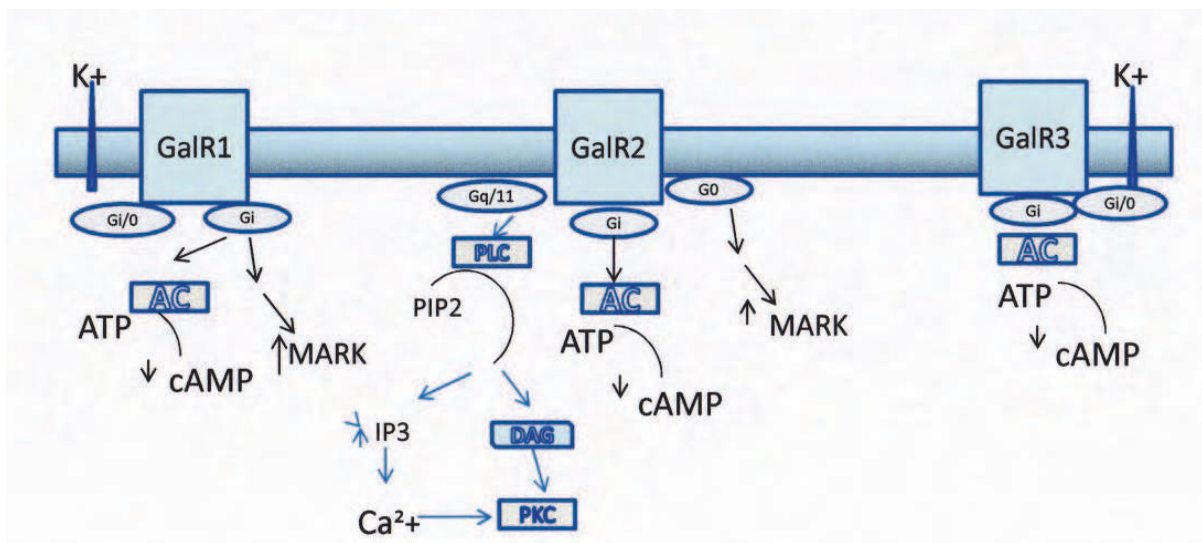

Fig. 2. Schematic illustration of the three galanin receptor subtypes and their intracellular transduction mechanisms. AC-adenyl cyclase , ATP-adenosine triphosphate, cAMP- cyclic adenosine monophosphate, DAG-diacyglycerol, IP3-inositol triphosphate, MAPK-mitogen activated protein kinase, PIP2-phosphatidyl 4,5-biposphate, PKC- protein kinase, PLC- phospholipase C.

2.1 Galanin in the early embryo

Galanin is one of the earliest neuropeptides to be expressed in the embryo. In the chicken embryo, galanin immunoreactive cells were first detected at E3.5 within the pharyngeal pouch region, the nodose ganglion, the primary sympathetic chain, the primitive splanchnic branches and the caudal portion of the Remark ganglion. These cells are derived from the neural crest. Indeed, galanin immunostaining appears at the same time as markers of neural crest cells. Transient galanin immunostaining was detected during the first week of development in cells displaying morphological features of migrating neuroblasts, but this expression domain had disappeared by E18 (Salvi, Vaccaro et al. 2001). At E4, galanin immunoreactivity was found in the spinal cord, medially in the motor column and in the intermediate zone. Neuroblasts appear coincident with galanin staining in the mesenchyme of the proventriculus/gizzard primordium (Salvi, Vaccaro et al. 1999; Salvi, Vaccaro et al. 2001). The precise role of galanin during chicken development remains unclear. The fact that in these experiments, galanin was present in undifferentiated or partially differentiated cells and the primitive sympathetic system well before these neurons reach their peripheral targets suggests that galanin has a developmental role in proliferation and migration.

Similar to the chicken, galanin-like immunoreactivity was detected in the mesenchyme and neural crest tissues of the early mouse embryo. At E10, we found that galanin-like immunoreactivity was readily detectable in the undifferentiated head and trunk mesenchyme (fig. 3) of mesenchymal or neural crest origin (Jones, Perumal et al. 2009), including the mesenchymal spiral ridges of the outflow tract of the heart and the endocardial cushions. The presence of galanin during these periods of morphogenesis
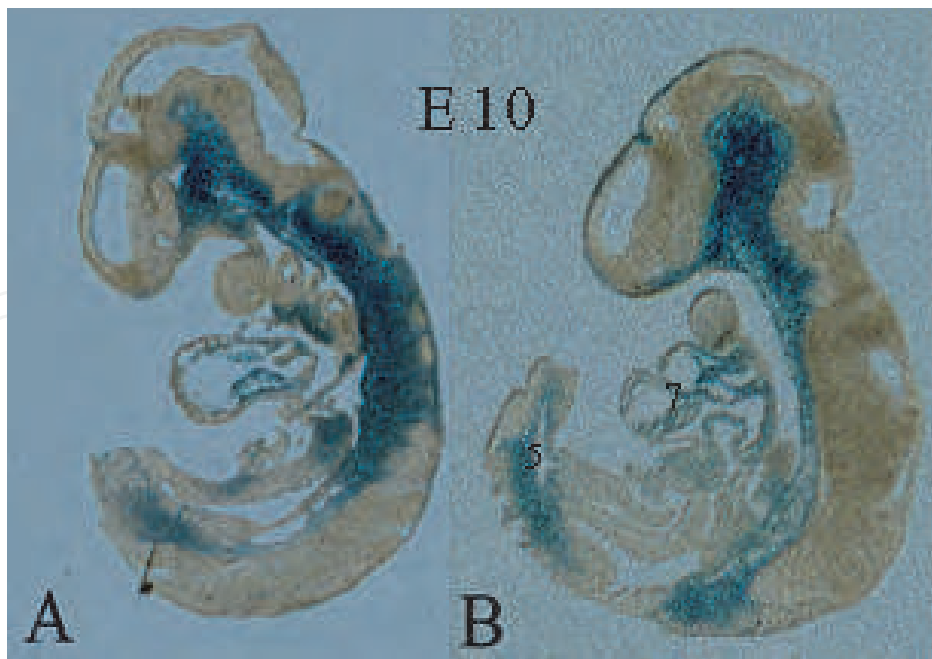
Fig. 3. Histochemistry profile of galanin like immunoreactivity in embryonic day 10 mouse embryo. A; sagittal and B; parasagittal section. Srong immonostaining for galanin is detected in the cephalic mesenchyme, trunk mesenchyme/somites, brachial arches, dorsal aorta and heart.

indicates a developmental role for this peptide in tissues of mesenchymal and neural crest origin in the early embryo. Galanin expression in mesenchymal cells during organogenesis was greater in tissues that depend on mesenchymal-epithelial interactions for their coordinated morphogenesis. Indeed, galanin staining is apparent during many instances of mesenchymal remodeling, e.g., during the formation of digits from limb buds, the formation of cartilage primordia in vertebrae and ribs, the formation of bones, the formation of the heart and in the mesenchyme of the kidney and genital organs (Jones, Perumal et al. 2009). It is surprising that at this early stage of development, galanin expression is largely outside the developing central nervous system. Thus, galanin might have different functions in the embryo and the adult. Although the functional significance of galanin expression in mesenchymal and neural crest cells is currently unclear, these data suggest a possible role for galanin in regulating stem/progenitor cell proliferation, migration and/or differentiation. This possibility is supported by our observation that galanin and its receptors are highly expressed in bone marrow mesenchymal stem cells (fig. 4) and facilitate cell migration both in vitro and in vivo (Louridas, Letourneau et al. 2009). Furthermore, the expression of galanin in neural crest cells may be relevant to our understanding of the molecular genetics of neuronal tumors. It has been shown that galanin and galanin receptors are expressed in cells of peripheral embryonic neuroectodermal tumors, such as glioblastomas and neuroblastomas (Berger, Tuechler et al. 2002; Berger, Santic et al. 2003; Berger, Santic et al. 2005). Perel et al. has suggested that galanin influences neuroblastoma development and tumor growth, counteracting differentiation as an autocrine/paracrine modulator (Perel, Amrein et al. 2002).

Galanin expression is also present in the mouse embryo at E7.5, during the late gastrulation stage. Here, galanin is abundantly expressed in the node (fig. 5) and primitive streak (Blum,
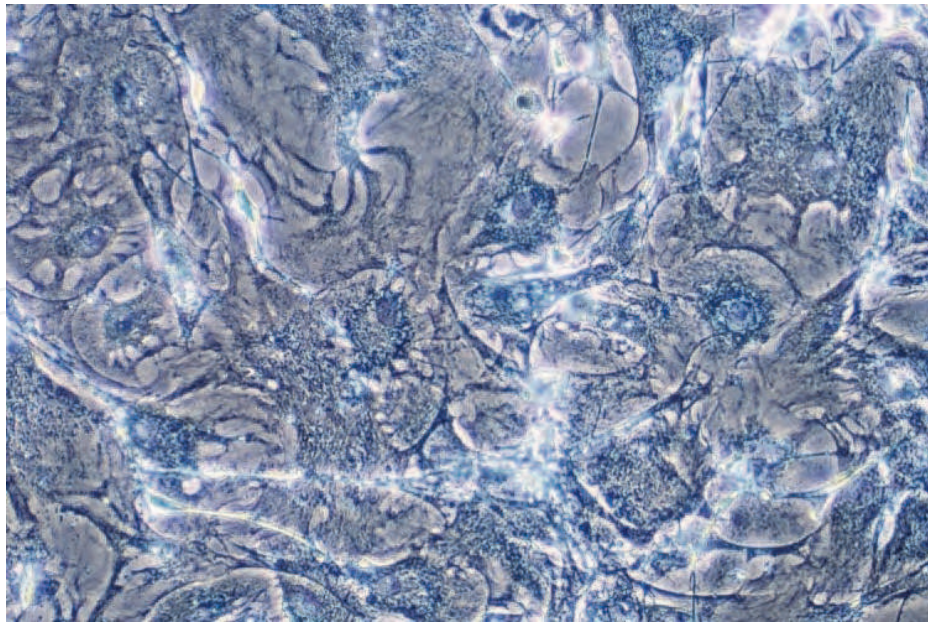
Fig. 4. Immunohistochemistry of bone marrow mesenchymal stem cells stained with a polyclonal galanin antibody. Strong staining is observed in both the cytoplasm and the nucleus of the cells.
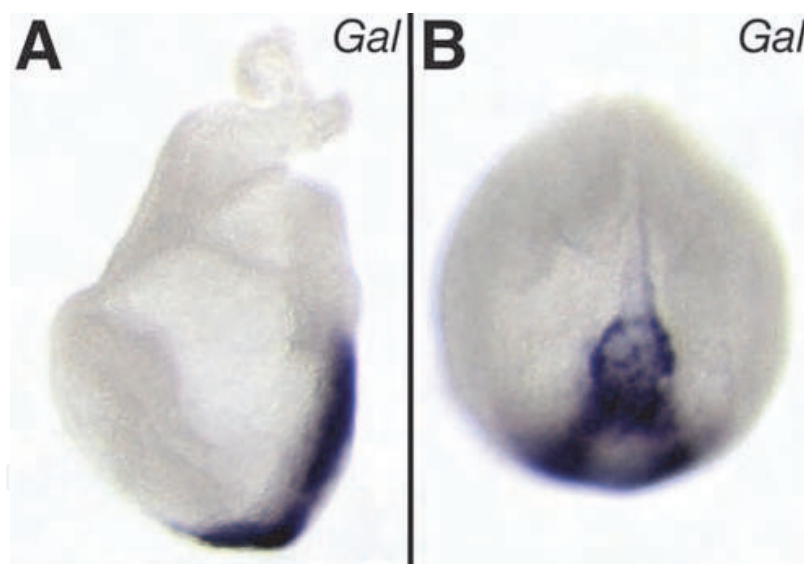

Fig. 5. E7.5 Galanin RNA in situ. A; is a lateral view of the embryo. B; is a distal view of the embryo. Copyright: This image is from Tamplin OJ, BMC Genomics 2008; 9(1):511, an open-access article, licensee BioMed Central Ltd

Andre et al. 2007) and thus represents a marker for the node and the notochord (Schweickert, Deissler et al. 2008; Tamplin, Kinzel et al. 2008). Shortly thereafter, at E8, expression in the primitive streak disappears. Nevertheless, the expression of a neuropeptide in the gastrula, that is, in the absence of any neural tissue, is quite surprising. In their studies, Tamplin et al. used Foxa2 mutant mice to identify novel marker genes for the node. Foxa2 is a forkhead transcription factor that is absolutely required for the formation of the node and the development of the three germ layers. Galanin expression

was completely absent in the Foxa2 mutant embryos, indicating that galanin is a target of the Foxa2 gene as well as a regulatory factor involved in patterning.

There are also reports of galanin mRNA expression in preimplantation embryos (Kang, Yeo et al. 2003; Kimber, Sneddon et al. 2008). In the first report (Kang, Yeo et al. 2003), the galanin gene sequence was examined for methylation changes in bovine embryos derived by in vitro fertilization (IVF). The authors observed that the galanin sequence maintained an undermethylated status until the morula stage. By the blastocyst stage, certain CpG sites became specifically methylated, which may be an epigenetic sign for the galanin gene to initiate a differentiation program. Such changes in DNA methylation status are very unusual in pre-implantation mouse development. Shortly after fertilization, the paternal pronucleus is subjected to active demethylation (Mayer, Niveleau et al. 2000), whereas the maternal genome simultaneously undergoes de novo methylation. Afterward, a passive replication-coupled demethylation process occurs in successive cleavage stages up to the blastocyst stage (Dean, Santos et al. 2001). This methylation reprogramming process allows the mouse zygote to gain totipotency and commence the formation of a new individual. In mammals, there are several periods of genome-wide reprogramming of methylation patterns during in vivo development. Typically, a substantial part of the genome is demethylated and then, after some time, remethylated in a cell- or tissue-specific pattern. Thus, galanin methylation appears to play a critical role in cell fate determination and differentiation during development. The study of epigenetic mechanisms underlying the establishment and maintenance of the pluripotent state as well as the differentiation process is an area of intense investigation in ESC biology.

In the second study mentioned above (Kimber, Sneddon et al. 2008), Kimber et al. examined the expression of a number of genes known to be critical for early mouse development in human pre-implantation embryos. Developmental expression of a number of these genes (e.g., galanin, OCT3/4, CDX2, NANOG) was similar to that seen in murine embryos. Galanin mRNA was expressed in the cleavage stages (8-cell stage onward), suggesting a role for galanin in early cell fate decision in human embryos, which may have important implications for IVF treatment and the derivation of human ESCs (hESCs). Indeed, the same group reported that galanin mRNA and protein were both expressed in undifferentiated hESCs and human embryonal carcinoma cells but down regulated upon differentiation, shortly after the down regulation of OCT3/4, Nanog and FoxD3 (El-Bareg et al. 2007), implicating communication between these pluripotent genes in the pre-implantation human embryo and hESCs.

2.2 Galanin in ESCs

ESCs derived from the blastocysts of pre-implantation embryos are pluripotent and have the capability to generate all of the differentiated cell types present in the embryo. The mechanisms regulating self-renewal and cell fate decisions in mammalian stem cells are poorly understood. As compared with differentiated cells, stem cells express a significantly higher number of genes (represented by expressed sequence tags) of unknown function. The properties that distinguish stem cells from other cell types are largely unknown, and the identification of signals that regulate stem cell differentiation remains fundamental to our understanding of cellular diversity. Thus, an important step in the characterization of ESCs will involve the identification of a set of ESC-specific genes that function as markers or contribute to unique regulatory pathways. One approach to identify these signals is to generate stem cell gene expression profiles. Anisimov et al. used the genomic technique of

serial analysis of gene expression (SAGE) to define the molecular bases of pluripotency and self-renewal (Anisimov, Tarasov et al. 2002). SAGE is a prominent technique for the quantitative and qualitative characterization of a cell's complete transcriptome (Velculescu, Madden et al. 1999). In their study, the authors performed SAGE on pluripotent mouse R1 embryonic stem cells, sequencing a total of 140,313 SAGE tags. Because of the sensitivity of SAGE and the potential quantification of tags from contaminating cells, they cultivated ESCs without feeder layers in the presence of conditioned medium and leukemia inhibitory factor (LIF). After five passages, R1 ESCs maintained pluripotency and the ability to differentiate into cardiac myocytes, hematopoietic and neuron-like cells. One of the most abundant sequences in this SAGE catalogue was galanin. To determine whether the abundance of galanin was a characteristic of ES cells in general or possibly a feature limited to R1 ESCs cultivated under these defined conditions, they constructed other SAGE libraries from embryonal carcinoma (EC) P19 cells, embryonic germ (EG) cells and embryonic stem (ES) cells under different cultivation conditions. Galanin was highly expressed in each of these lines, indicating that high galanin expression is a distinguishing molecular feature of ESCs (Tarasov, Tarasova et al. 2002).

In addition to galanin, all three galanin receptors (GalR1, GalR2 and GalR3) are expressed in mouse R1 ESCs. Quantification of their relative abundances showed that GalR1 is barely detectable in R1 ESCs, while GalR2 and GalR3 are relatively abundant (GalR2 & GalR3 >> GalR1). Similarly, GalR1 is almost undetectable in P19 EC cells but highly abundant in fetal tissues (E16). GalR2 and GalR3 have similar levels of expression in P19 EC and R1 ESCs, and both receptors are widely distributed among fetal tissues (Tarasov, Tarasova et al. 2002). Unlike GalR1 and GalR3, the biological activity of GalR2 is exerted through activation of Gq and phospholipase C. It has also been suggested to play a prominent role during nervous system development (Burazin, Larm et al. 2000). Thus, the presence of galanin transcripts and the relative abundance of GalR2 and GalR3 in ES and EC cells suggest that galanin may be biologically active in ESCs.

Galanin function has been associated with LIF signaling. Addition of LIF into primary dorsal root ganglia (DRG) cultures significantly upregulated galanin expression (Ozturk and Tonge 2001). Similarly, LIF knockout mice have significantly lower levels of galanin (Sun and Zigmond 1996; Sun and Zigmond 1996). To determine whether the prominence of galanin in ESCs is mediated through an interaction with LIF, a series of further experiments were performed in which the medium containing LIF was substituted with non-conditioned maintenance medium without LIF. The absence of LIF actually increased galanin expression in R1 cells. Similarly, removing LIF had no effect on galanin expression in cultured hESCs (El-Bareg et al. 2007; Kimber, Sneddon et al. 2008), indicating that the abundance of galanin transcripts in ESCs is not regulated by LIF.

Several differences between human and mouse ESCs have been identified, including an inactive LIF pathway in human ESCs. Similar to the mouse, the transcriptome profile of hESCs was obtained using SAGE (Richards, Tan et al. 2004). A list of candidate marker genes responsible for stemness in human ESCs has also been created, with galanin highlighted as one of the most abundant genes (Richards, Tan et al. 2004). Transcription factors with a defined role in the maintenance of pluripotency and whose expression is downregulated upon differentiation, including POU5F1 (Oct3/4), SOX2, Galanin, REX1, NANOG, and FLJ10713, were previously identified in mouse ESCs (Anisimov, Tarasov et al. 2002; Ramalho-Santos, Yoon et al. 2002; Mitsui, Tokuzawa et al. 2003).

Using a large-scale oligonucleotide microarray, the profiles of 6 available human ESC lines were analyzed. The expression of defined genes was confirmed by reverse transcriptase polymerase chain reaction (RT-PCR), immunohistochemistry, focused microarrays and comparison to various databases maintained at the National Cancer Institute (Bhattacharya, Miura et al. 2004; (Zeng, Miura et al. 2004). A comparison of overexpressed genes identified 92 genes common to all six lines. These 92 genes constitute a molecular signature of "stemness" in human ESCs. Galanin was the most abundant, along with Oct3/4, Nanog, Sox2 and FOXD3. However, the exact molecular mechanisms involved in self-renewal and pluripotency are still not very clear.

In many respects, germ cell tumorigenesis resembles early embryogenesis. Embryonal carcinomas represent a histologic subgroup of testicular germ cell tumors, and EC cells may follow a differentiation trajectory in a manner similar to early embryogenesis. Using microarray analysis, the transcriptome of neoplastic tissues from the human testis was analyzed by Skotheim et al. (Skotheim, Lind et al. 2005). Selection for genes highly expressed in the undifferentiated, pluripotent embryonal carcinomas identified the major pluripotency markers, including Galanin, POU5F1(Oct3/4), NANOG, DPPA4. Again, Galanin was the most highly expressed gene. Galanin and POU5F1 were both up regulated at the protein level and thereby validated as diagnostic markers for undifferentiated tumor cells.

Preliminary data support the hypothesis that galanin exerts an effect on self-renewal and pluripotency of ESCs along with POU5FI, NANOG and DPPA4 because it is temporarily down regulated upon ESC differentiation and is also more abundant in undifferentiated embryonal carcinomas relative to differentiated carcinomas. Differential DNA methylation of specific sites in the galanin gene might represent an epigenetic signal for the galanin gene to initiate a differentiation program. This occurrence may explain why galanin continues to be expressed in somatic cells of neural crest and mesenchymal origin in the early embryo. Both de novo methylation and maintenance DNA methylation are critical for early development, but they are required for differentiation rather than maintenance of the undifferentiated state. Human ESCs have been shown to possess a unique DNA methylation signature as compared with differentiated cells and cancer cells (Bibikova, Chudin et al. 2006; Meissner, Mikkelsen et al. 2008; Amabile and Meissner 2009; Ball, Li et al. 2009; Meissner 2010), which supports the concept that a specific DNA methylation pattern may contribute to the pluripotent state. In particular, the pluripotency-associated genes Galanin, POU5F1(Oct3/4), NANOG and DPPA4 are largely unmethylated in ESCs and methylated in differentiated cells.

Understanding the epigenetic regulation of ESCs will help to shed light on the molecular basis of normal development as well as the abnormal processes that underlie cancer.

3. Conclusion

In conclusion, the neuroendocrine peptide galanin is one of the most highly expressed genes in both human and mouse ESCs and the embryonic tissues of many species. Galanin is thus considered a marker of "stemness" and pluripotency. All three galanin receptors are present in ESCs, suggesting that the peptide may be biologically active. There are enough indications to suggest a highly dynamic role of galanin in ESCs and in committing the fate of ES cells. The variety of cellular effect of galanin may depend on the environment surrounding the cells and possibly differential activation of its receptors. The switch from self-renewal to differentiation of ESCs might be triggered by a combination of other signals

and coordinated changes in recruitment of epigenetic modulators and transcription factors to the promoter region. The strength of the intracellular signaling may affect the negative or positive regulatory elements of the galanin gene to use different intracellular pathways to mediate different cell function in ES cells.

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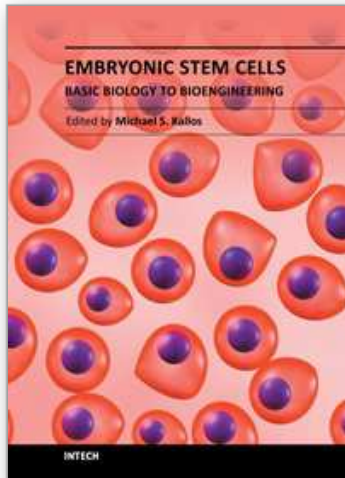
Embryonic Stem Cells - Basic Biology to Bioengineering

Edited by Prof. Michael Kallos

Embryonic stem cells are one of the key building blocks of the emerging multidisciplinary field of regenerative medicine, and discoveries and new technology related to embryonic stem cells are being made at an ever increasing rate. This book provides a snapshot of some of the research occurring across a wide range of areas related to embryonic stem cells, including new methods, tools and technologies; new understandings about the molecular biology and pluripotency of these cells; as well as new uses for and sources of embryonic stem cells. The book will serve as a valuable resource for engineers, scientists, and clinicians as well as students in a wide range of disciplines.

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