Molecular and Cellular Endocrinology 385 (2014) 2–17

Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

journal homepage: www.elsevier.com/locate/mce

Review

Pituitary stem cells: Where do we stand?

Hugo Vankelecom [a,*], Jianghai Chen [b,**]

[a] Department of Development and Regeneration, Cluster Stem Cell Biology and Embryology, Research Unit of Stem Cell Research, University of Leuven (KU Leuven), B-3000 Leuven, Belgium
[b] Department of Hand Surgery, Tongji Medical College, Union Hospital, Huazhong University of Science & Technology (HUST), Wuhan, Hubei 430022, PR China

ARTICLE INFO

Article history:
Available online 28 August 2013

Keywords:
Pituitary stem cells
Side population
Sox2
Prop1
Regeneration
Gonadotropes

ABSTRACT

Some 5 years ago, the stem cells of the adult pituitary gland were discovered. Subsequent in-depth characterization revealed expression of several stemness markers and embryo-typical factors. Now, the quest is open to decipher their role in the gland.

When and how pituitary stem cells differentiate to contribute to the mature hormone-producing cell populations is not known. New research models support their involvement in cell regeneration after injury in the gland, and suggest a possible role in pituitary tumor formation. From their expression phenotype, pituitary stem cells seem to re-use embryonic developmental programs during the creation of new hormonal cells.

Here, we will review the latest progression in the domain of pituitary stem cells, including the uncovering of some new molecular flavors and of the first potential functions. Eventually, we will speculate on their differentiation programs towards hormonal cells, with a particular focus on gonadotropes.

Contents

Abbreviations: ACE, angiotensin-converting enzyme; ACP, adamantinomatous craniopharyngioma; ACTH, adrenocorticotropic hormone; AP, anterior pituitary; β-catnc, nucleocytoplasmic β-catenin; BMP, bone-morphogenetic protein; CSC, cancer stem cells; DT, diphtheria toxin; e, embryonic day; EB, embryoid body; (e)GFP, (enhanced) green fluorescent protein; EMT, epithelial–mesenchymal transition; ES, embryonic stem; (b)FGF, (basic) fibroblast growth factor; FS, folliculostellate; FSH, follicle-stimulating hormone; GFRa2, glial cell line-derived neurotrophic factor receptor alpha 2; GH, growth hormone; GnRH, gonadotropin-releasing hormone; GSU, glycoprotein hormone subunit; Hesx1, homeobox gene expressed in ES cells 1; IL, intermediate lobe; ISH, *in situ* hybridization; Klf4, Krüppel-like factor 4; LH, luteinizing hormone; LIF, leukemia-inhibitory factor; PRL, prolactin; Prop1, Prophet of Pit1; RA, retinoic acid; Rb, retinoblastoma protein; RP, Rathke's pouch; Sca1, stem cell antigen 1; (SC-)SP, (stem cell-)side population; Sdf1, stromal-derived factor 1; Sf1, steroidogenic factor 1; Shh, sonic hedgehog; Sox2, sex-determining region Y-related high mobility group box gene 2; TSH, thyroid-stimulating hormone; Wnt, Wingless-type MMTV integration site.

* Corresponding author. Address: Department of Development and Regeneration, Cluster Stem Cell Biology and Embryology, Research Unit of Stem Cell Research, KU Leuven, Campus Gasthuisberg O&N4-804, Herestraat 49, B-3000 Leuven, Belgium. Tel.: +32 16 330692; fax: +32 16 330642.

** Co-corresponding author. Address: Department of Hand Surgery, Tongji Medical College, Union Hospital, Huazhong University of Science & Technology (HUST), Jiefang Avenue 1277#, Wuhan, Hubei 430022, PR China. Tel.: +86 27 8535 1628.

E-mail addresses: Hugo.Vankelecom@med.kuleuven.be (H. Vankelecom), chenjianghai2002@hotmail.com (J. Chen).

0303-7207/$ - see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.mce.2013.08.018

1. Introduction

The pituitary gland constitutes the hub of the endocrine system. It translates multifarious hypothalamic and peripheral inputs into the release of hormones that impact on downstream endocrine glands, thus regulating the core organismal processes of growth, metabolism, procreation, and coping with immune challenges and stress. Production of hormones occurs in dedicated cell types primarily present in the anterior lobe of the gland (anterior pituitary or AP). Growth hormone (GH) is produced by somatotropes, prolactin (PRL) by lactotropes, adrenocorticotropic hormone (ACTH) by corticotropes, thyroid-stimulating hormone (TSH) by thyrotropes, and luteinizing hormone (LH) and/or follicle-stimulating hormone (FSH) by gonadotropes. Plenty is known about the developmental programs of these different cell types during the embryogenetic formation of the gland (reviewed in Vankelecom, 2010; Zhu et al., 2007). However, how these hormonal cells are formed or renewed during postnatal life remains largely unsolved.

In other tissues, new cells can be generated by resident stem cells during conditions of homeostatic turnover, plastic cell adaptation to the body's demands and/or regeneration after tissue damage (Alvarez-Buylla and Lim, 2004; Rando, 2006; Slack, 2008). Thus, stem cells possess multipotent differentiation capacity to generate the desired tissue cell types. During this process, stem cells first give rise to daughter (progenitor) cells that proliferate to expand as a pool of transit-amplifying cells, which further commit to precursor cells that differentiate towards the specific, required tissue cells (Alvarez-Buylla and Lim, 2004; Rando, 2006; Slack, 2008; Vankelecom, 2007b; Vankelecom and Gremeaux, 2010). Stem cells must be sustained as long as possible in life, and therefore regularly generate new stem cells by self-renewal. They are typically housed in a specialized microenvironment of the tissue, the niche, which regulates their maintenance, self-renewal, fate determination and reaction to external influences.

About 10 years ago, the first more-persuasive indications were provided that the pituitary gland, like other adult tissues, contains a putative population of stem/progenitor cells (further simplified to 'stem cells') (Chen et al., 2005). After a succeeding lag period, several groups then almost simultaneously reported further convincing evidence that, against much skepticism, stem cells indeed exist in the pituitary (Chen et al., 2009; Fauquier et al., 2008; Garcia-Lavandeira et al., 2009; Gleiberman et al., 2008). Collectively, these studies concluded that pituitary stem cells express several stemness markers (such as Sox2) and pituitary-embryonic factors (such as Prop1), and that they prominently occupy the marginal zone around the cleft, the residual lumen of the adenohypophyseal primordium Rathke's pouch (RP) (reviewed in Vankelecom, 2010). In addition to this marginal-zone location, clusters of Sox2-immunoreactive (Sox2+) cells were also observed scattered within the AP parenchyma (Chen et al., 2009; Fauquier et al., 2008; Fu et al., 2012; Garcia-Lavandeira et al., 2009; Gleiberman et al., 2008; Gremeaux et al., 2012), suggesting the existence of multiple stem cell niches which would be favorable for dynamic and/or subtle cell adaptations. Recent studies have shown that the parenchymal Sox2+ cell clusters may be connected to the marginal-zone cells (Gremeaux et al., 2012; Mollard et al., 2012). The pituitary stem cell niches may therefore not represent isolated focal spots, but establish a three-dimensional cooperating network throughout the gland, in line with the other (homotypic) networks formed by the hormonal cells in the pituitary (as shown for somatotropes, lactotropes, corticotropes and gonadotropes) (Le Tissier et al., 2012; Mollard et al., 2012).

In clear contrast to the considerable evidence that cells with stem cell phenotype exist in the pituitary, not much is known yet about their functional position and significance. Actually, this conundrum not only applies to the pituitary, but to many other adult tissues. For instance, neural stem cells have been identified in the postnatal brain many more years ago, and hence are characterized in more detail than pituitary stem cells. Nonetheless, their function in neurogenesis during turnover and disease is still very enigmatic (Alvarez-Buylla and Lim, 2004; Kriegstein and Alvarez-Buylla, 2009; von Bohlen und Halbach, 2011). Regarding the pituitary stem cells, studies are only now beginning to address their role and participation, particularly in processes of postnatal pituitary maturation, repair and pathology.

Here, we will follow up on the episode of pituitary stem cell identification (2005–2009), focusing on new and/or overlooked markers and on the first uncoverings of their roles. We will apply these elements to refine the previous tentative model on the pituitary stem cell compartment and its biology (see Vankelecom, 2010). Finally, we will speculate on the developmental programs that may take place during the postnatal conversion of stem cells into new mature endocrine cells. In the context of this review series' scope, we will particularly focus on the specification towards gonadotropes.

2. Update on the pituitary stem cell saga following the discovery period

2.1. Short overview and commentary on the earlier pituitary stem cell phenotype

The previously characterized molecular phenotype and topography of the pituitary stem cells have amply been described in earlier reviews (Castinetti et al., 2011; Florio, 2011; Nassiri et al., 2013; Vankelecom, 2010; Vankelecom and Gremeaux, 2010). In general, the molecular phenotype can be divided into a stemness part and a (pituitary-)embryonic share.

Several factors attributed to stem cells in other tissues, have been detected in the pituitary stem cell compartment through gene expression and immunostaining analysis. Amongst these, Sox2, being unanimously detected, occupies a central position (Fig. 1). The topographical phenotype of Sox2+ cells as well as the functional significance of the Sox2 transcription factor itself were subject of several recent investigations (see below, in particular Sections 2.3 and 2.4).

In the general belief that stem cells in adult tissues represent enduring embryonic cell phenotypes (Alvarez-Buylla and Lim, 2004; Jensen et al., 2005; Roskams, 2006; Slack, 2008; Wagers and Conboy, 2005), several groups looked for the presence of factors playing a role in pituitary embryonic development. An extended review on this embryonic aspect of adult pituitary stem cells has recently been published (Vankelecom, 2010). In particular, as confirmed by most groups, the pituitary-specific, embryonically important transcription factor Prop1 is expressed in adult pituitary stem cells, perhaps not continuously but at least during