Molecular and Cellular Endocrinology 445 (2017) 14–26

Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

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

Regulation of pituitary stem cells by epithelial to mesenchymal transition events and signaling pathways

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ARTICLE INFO

Article history:
Received 9 August 2016
Received in revised form
15 September 2016
Accepted 16 September 2016
Available online 17 September 2016

Keywords:
Pituitary
Stem cells
SOX2
PROP1
EMT
Extracellular matrix

ABSTRACT

The anterior pituitary gland is comprised of specialized cell-types that produce and secrete polypeptide hormones in response to hypothalamic input and feedback from target organs. These specialized cells arise from stem cells that express SOX2 and the pituitary transcription factor PROP1, which is necessary to establish the stem cell pool and promote an epithelial to mesenchymal-like transition, releasing progenitors from the niche. The adult anterior pituitary responds to physiological challenge by mobilizing the SOX2-expressing progenitor pool and producing additional hormone-producing cells. Knowledge of the role of signaling pathways and extracellular matrix components in these processes may lead to improvements in the efficiency of differentiation of embryonic stem cells or induced pluripotent stem cells into hormone producing cells *in vitro*. Advances in our basic understanding of pituitary stem cell regulation and differentiation may lead to improved diagnosis and treatment for patients with hypopituitarism.

1. Introduction

The ability of the pituitary gland to increase hormone production in times of demand had long suggested the existence of postnatal pituitary stem cells, and interest in pituitary stem cell biology has intensified since 2008 when SOX2-expressing cells in adult pituitary glands were first shown to possess stem cell capacity to self-renew and differentiate into all of the major hormone-producing cell types of the pituitary gland *in vitro* (Fauquier et al., 2008). Since then, several major advances have taken place, and these have been the focus of recent review articles (Suga, 2016; Yoshida et al., 2016a, 2016b; Garcia-Lavandeira et al., 2015; Willems and Vankelecom, 2014). *In vitro* differentiation of both human and mouse embryonic stem (ES) cells into pituitary hormone producing cells in culture has been successfully developed and improved upon in recent years, shedding light on mechanisms which could stimulate differentiation of pituitary stem cells *in vivo* (Zimmer et al., 2016; Suga et al., 2011; Ozone et al., 2016; Dincer et al., 2013). The composition of the stem cell niche is being investigated, and an epithelial to mesenchymal (EMT)-like process was shown to drive migration of progenitors out of the niche (Perez Millan et al., 2016). Pathways regulating cell turnover are being identified (Diaz-Rodriguez et al., 2012), and the limitations of self-renewal over the life of the animal are emerging (Willems et al., 2016). In this review, after an overview of pituitary development, we concentrate on the most recent advances regarding the role of the transcription factor PROP1 in establishing stem cell pools and driving the EMT-like transition, the role of signaling pathways, and the potential role of mesenchymal stem cells. We also cover the challenges of stem cell therapeutics and unanswered questions that may be the focus of future studies. The role of cancer stem cells in pituitary adenomas are the subject of a separate review in this issue (J.P. Martinez-Barbera and colleagues, this Issue).

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http://dx.doi.org/10.1016/j.mce.2016.09.016
0303-7207/

2. Pituitary organogenesis: formation of the mature gland from multiple embryonic origins

2.1. Contributions of surface ectoderm and neural ectoderm

The pituitary gland is an endocrine organ found only in vertebrates, and aspects of its development and the nature of the specialized hormone-producing cell types are evolutionarily conserved across vertebrate species (de Beer, 1924). Thus, studies in birds, amphibians, fish, and mammals have informed our understanding of cell specification and pituitary development (De Groef et al., 2008; Pogoda and Hammerschmidt, 2009; Kawamura et al., 2002; Rizzoti, 2015). For example, the roles of FGF, BMP, SHH and WNT signaling pathways in pituitary development have been established in multiple species. Fate mapping studies in several different species have revealed that the mature pituitary gland is composed of cells that originate from the surface (oral) ectoderm, the neural ectoderm, and the cranial mesenchyme. The oral ectoderm forms the anterior and intermediate lobes, and the neural ectoderm forms the posterior lobe, while the cranial mesenchyme forms vasculature and connective tissue within and surrounding the mature gland.

Craniofacial placodes are specific regions of the non-neural surface ectoderm that thicken in relation to the adjacent ectoderm, and will give rise to the pituitary gland as well as several other craniofacial structures. The pituitary, lens, olfactory, otic, trigeminal and epibranchial placodes (in mammals) arise from the preplacodal region, which is a region of the surface ectoderm adjacent to the neural ectoderm (Fig. 1). The early placodes utilize common signaling pathways and genetic networks as they form the initial placode stages, before diverging and activating unique placode-specific programs to form the distinct tissue systems (Singh and Groves, 2016; McCabe and Bronner-Fraser, 2009; Brunskill et al., 2014). Thus, these placode expression studies provide candidate genes for regulation of pituitary development, and some of the mechanisms that underlie stem cell regulation in other craniofacial placodes may apply to the pituitary gland.

The pituitary (or adenohypophyseal) placode is a thickening of the oral ectoderm at the roof of the mouth that invaginates to produce Rathke's pouch (reviewed in (Rizzoti, 2015)) (Fig. 2). It is in juxtaposition to the neural ectoderm of the ventral diencephalon, which evaginates to form the infundibulum (pituitary stalk) and posterior lobe (neurohypophysis or *pars nervosa*) (Pearson and Placzek, 2013). The infundibular region of the ventral diencephalon expresses the morphogenetic proteins BMP4, FGF8, and FGF10, which act as a signaling center, or pituitary organizer, for the induction and proliferation of Rathke's pouch (reviewed in (Davis et al., 2013)). SHH is initially expressed in the ventral midline throughout the neural tube; however, in the infundibular region of the ventral diencephalon, SHH expression is inhibited by BMP signaling and by TBX2 and TBX3. Persistent SHH expression in the infundibular region results in loss of the pituitary organizer and reduction or loss of Rathke's pouch (Manning et al., 2006; Trowe et al., 2013). The pituitary organizer, especially FGF signaling, also acts as a chemoattractant for axons of oxytocin and vasopressin expressing neurons located in the paraventricular nucleus of the hypothalamus (Liu et al., 2013). The progenitor cells within the infundibular region give rise to the pituicytes, the glial-like cells of the posterior lobe, and Notch signaling through *Hes1* and *Hes5* is necessary for promoting pituicyte fate specification (Goto et al., 2015). The posterior lobe and pituitary stalk are continuous with the median eminence of the hypothalamus, which releases hypothalamic hormones into the hypophyseal portal system and regulates anterior pituitary hormone secretion.

FGF signaling from the pituitary organizer promotes the survival of the pituitary progenitor cells in Rathke's pouch (De Moerlooze et al., 2000; Ohuchi et al., 2000; Takuma et al., 1998). The area of highest proliferation in Rathke's pouch is at the dorsal aspect, closest to the infundibular signaling center. This region of Rathke's pouch contains the SOX2-expressing stem cells at E12.5 and E14.5 in mouse development. As the Rathke's pouch continues to invaginate upwards, the base of the pouch will close off and completely separate from the oral ectoderm, followed by the condensation of the sphenoid cartilage between the two ectodermal structures. The dorsal (top) side of the pouch forms the intermediate lobe while the ventral (bottom) side forms the anterior lobe. The residue of Rathke's cleft defines the separation between the lobes in rodents, and it can appear as a lumen in histological sections due to the shrinkage of the tissue during processing. In humans and some other species, the intermediate lobe is not distinct, but residual cleft tissue can be found. This tissue is thought to be the stem cell niche and is referred to as the marginal zone. There is an EMT-like transition, including a reduction in E-cadherin expression at the ventral aspect of the Rathke's cleft, as anterior lobe progenitor cells begin to differentiate and delaminate ventrally and migrate laterally from the lumen, causing the expansion of the parenchyma of the anterior lobe (Perez Millan et al., 2016; Ward et al., 2005; Himes and Raetzman, 2009).

2.2. Contributions of the notochord and mesenchyme

Studies of pituitary development have focused on the nature of the signaling between the ventral diencephalon and Rathke's pouch. However, both the notochord and the mesenchyme that surrounds the developing pituitary gland are additional sources of important signaling molecules, which have the potential to

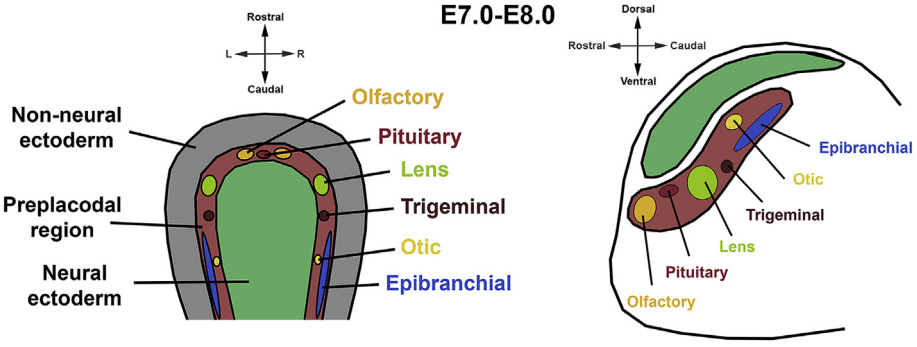

Fig. 1. The preplacodal region is the interface between the neural and surface ectoderms. Interaction between the surface and neural ectoderm gives rise to the preplacodal region between E7.0-E8.0 in mouse (~E15-19 in humans, ~E8.5–9.0 in rats), from which multiple craniofacial tissues are ultimately derived.