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Journal of Endocrinology and Disorders

Beyene Petros, J Endocrinology and Disorders

Open Article

Commentary

# Neuro Endocrine Physiology: Pineal Gland Development

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**Received date: January 17 2018; Accepted date : January 27 2018; Published date: February 02, 2018**

**Citation for this Article :** Beyene Petros**,**Silvia Bensari**,** Neuro Endocrine Physiology: Pineal Gland Development J. Endocrinology and Disorders. **Doi: 10.31579/2640-1045/023**



The adult pineal gland is composed of pinealocytes, astrocytes, microglia, and other interstitial cells that have been described in detail. However, factors that contribute to pineal development have not been fully elucidated, nor have pineal cell lineages been well characterized. We applied systematic double, triple and quadruple labeling of cell-specific markers on prenatal, postnatal and mature rat pineal gland tissue combined with confocal microscopy to provide a comprehensive view of the cellular dynamics and cell lineages that contribute to pineal gland development. The pineal gland begins as an evagination of neuroepithelium in the roof of the third ventricle. The pineal primordium initially consists of radially aligned Pax6+ precursor cells that express vimentin and divide at the ventricular lumen. After the tubular neuroepithelium fuses, the distribution of Pax6+ cells transitions to include rosette-like structures and later, dispersed cells. In the developing gland all dividing cells express Pax6, indicating that Pax6+ precursor cells generate pinealocytes and some interstitial cells. The density of Pax6+ cells decreases across pineal development as a result of cellular differentiation and microglial phagocytosis, but Pax6+ cells remain in the adult gland as a distinct population. Microglial colonization begins after pineal recess formation. Microglial phagocytosis of Pax6+ cells is not common at early stages but increases as microglia colonize the gland. In the postnatal gland microglia affiliate with Tuj1+ nerve fibers, IB4+ blood vessels, and Pax6+ cells. We demonstrate that microglia engulf Pax6+ cells, nerve fibers, and blood vessel-related elements, but not pinealocytes. We conclude that microglia play a role in pineal gland formation and homeostasis by regulating the precursor cell population, remodeling blood vessels and pruning sympathetic nerve fibers.

In vertebrates, the pineal gland effects and regulates the circadian timing system by transducing environmental light into an internal signal, the nocturnal melatonin [1]. The pineal gland develops from a committed area of the neuroepithelium that lines the roof of the third ventricle in the prenatal brain, and its maturation continues postnatally. During the first postnatal week the rat pineal gland begins responding in a rhythmic fashion to sympathetic innervation from the superior cervical ganglia [2,3], which relay circadian information from the suprachiasmatic nuclei (SCN). While a growing body of work has identified cellular and transcriptional mechanisms required for pineal ontogeny, additional factors that contribute to pineal development and homeostasis have not been fully elucidated.

A dynamic and intricate regulatory network of transcription factors drives the definition and maintenance of pineal phenotype [4–10]. The homeobox transcription factors Pax6, Otx2 and Lhx9 are necessary for proper pineal gland formation [11–16]. Pax6 is considered one of the earliest phenotype determinants responsible for regulating pinealocyte specification and prenatal proliferation since the pineal gland fails to develop in the absence of functional Pax6. Rath et al. demonstrated that Pax6 mRNA expression peaks in the developing rat pineal gland on embryonic (E) day 18, followed by a rapid perinatal decline [17].

However, the cells that express the Pax6 protein have not been fully characterized in terms of their location, distribution, function or relationship with other cells in the pineal gland. In addition, the Pax6+ cell lineage fate throughout pineal development has not been well delineated. In this study we present the ontogeny of the Pax6+ cell lineage in the rat pineal gland, and how interactions between Pax6+ cells and other pineal gland cell types contribute to gland formation and homeostasis.

The mature pineal gland is considered a relatively homogeneous organ that is composed of a small set of well-defined cell types. Approximately 95% of the cells are pinealocytes, with the remainder consisting mainly of interstitial cells–astrocytes and microglia–embedded in a network of blood vessels and nerve fibers [18]. The concept of pinealocyte homogeneity, however, is currently being reevaluated [10,19]. Microglia have been identified as one of the pineal interstitial cell types via OX6 (MHCII), OX42 (CD11b), IL-1β, ED1 (CD68), and TNF-R1 expression, among other markers [20–26]. Microglia have been reported to play several roles in the pineal gland, including regulation of pinealocyte neurites in a cytokine-dependent manner [27–30]; serving as antigen-presenting cells [20,22]; sensing physical injury, bacteria, and hypoxia [21,31,32], and modulating pineal melatonin [31–35]. Our data expand the repertoire of microglial functions in the developing and adult pineal gland. We show that microglia phagocytose Pax6+ cells, especially in the adult gland, and also engulf blood vessel and nerve fiber elements. Our data provide a novel perspective on the cellular dynamics that shape formation of the developing pineal gland and homeostasis in the mature pineal gland.

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