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Neurogenesis in deer antlers: Stem-cell-based development and regeneration

Abstract

Deer antlers are the only mammalian accessory organs capable of complete annual regeneration, and they provide a unique model for studying neurogenesis and tissue regeneration. The process involves the coordinated regeneration of multiple tissue types, with nerves playing a pivotal role in sensory perception and in tissue function. In this study, current knowledge on neurogenesis in deer antlers was synthesized, emphasizing stem-cell-based development and regeneration mechanisms. The types of stem cells involved, the process of neurogenesis, and nerve regeneration, are discussed, and the potential biomedical applications of this natural model are explored.

Keywords: Deer antlers; Neurogenesis; Stem cells; Regeneration; Nerve regeneration; Biomedical applications.

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Introduction

Deer antlers have long captivated the scientific community as an exceptional model of mammalian regeneration because of their unparalleled ability to undergo complete, cyclical regrowth, annually [1]. This process is not merely a simple regrowth of bone and cartilage, but it involves the highly coordinated regeneration of multiple, complex tissue types, including skin, blood vessels, cartilage, and bone, and notably, a fully functional peripheral nervous system. The intricate network of sensory nerves within the antler is essential for spatial awareness, detection of physical contact, and overall behavioral interactions with the environment [2,3]. Consequently, deer antlers are a unique and powerful natural model for investigating the fundamental mechanisms underlying neurogenesis, axon guidance, and peripheral nerve regeneration in the context of rapid and extensive appendage regrowth.

The regeneration process is orchestrated by a specialized structure, the antler blastema, a pool of progenitor cells located at the tip of the growing antler [4]. Studies have reported that the blastema has a remarkable degree of cellular plasticity, giving rise to all lineages required to reconstruct the antler. A critical aspect of this process is precise re-innervation of the newly forming antler tissue.

In addition to direct nerve repair, the antler model has broad implications for tissue engineering and complex organ regeneration. It demonstrates how a complex organotypic structure integrates bone, vascular supply, and neural networks, and it can be rebuilt from a progenitor cell mass. Studying the spatiotemporal regulation of growth factors and epigenetic control during antler growth could inform efforts to engineer composite tissues or stimulate endogenous repair mechanisms in mammals that have lost this capacity.

Thus, periodic regeneration of the deer antler, encompassing its sophisticated nervous system, is one of the most compelling examples of perfect mammalian regeneration. This intensive study bridges developmental biology, neuroscience, and regenerative medicine. Unlocking its secrets promises not only to deepen understanding of fundamental biological principles, but also to catalyze the development of groundbreaking clinical interventions for nerve injury, limb loss, and beyond, bringing the paradigm of true regenerative medicine closer to reality.

Regeneration of deer antlers

Deer antlers are the only mammalian organs capable of complete and periodic regeneration [2]. Antlers are located on the frontal bone (the bone forming the forehead and the upper parts of the orbits), and there is stem-cell-based organogenesis, annual casting, and *de novo* regeneration. These processes are initiated at the antler pedicle, which is a permanent bony structure on the skull. Each year, old antlers are shed and new antlers rapidly grow from the pedicle, reaching impressive sizes within a few months. Regeneration involves the coordinated growth of skin, blood vessels, nerves, cartilage, and bone, making it a multifaceted biological phenomenon [1,4].

Figure 1: Antler regeneration cycle. In spring, bony antlers drop from their pedicle (permanent bony protuberance). Velvet antler immediately regenerates. In late spring and early summer, there is rapid antler growth and antlers are covered with velvet skin in their growing phase. In autumn, antlers become completely calcified and the covering skin begins to shed. In winter, dead bony antlers are attached to their living pedicles, and they eventually cast in spring of the next year, triggering a new round of antler regeneration [5]. Copyright © Frontiers in Bioscience. Published by Frontiers in Bioscience.

Neurogenesis and nerve regeneration in deer antlers

Neurogenesis in growing antlers

Neurogenesis in regenerating deer antlers is a precisely orchestrated process that begins within the highly specialized microenvironment of the antler pedicle [6-8]. The growing antler is densely innervated by sensory nerves that originate from the trigeminal nerve, which is the principal cranial nerve responsible for facial sensations. Specifically, the supraorbital and temporal branches of the trigeminal nerve provide primary axonal input [3,9,10]. After injury or casting of an old antler, these nerves undergo a robust regenerative response. Axons from the proximal nerve stumps in the pedicle extend distally, navigating through the rapidly proliferating mesenchyme of the antler blastema to re-establish a complete sensory map of the new antler structure.

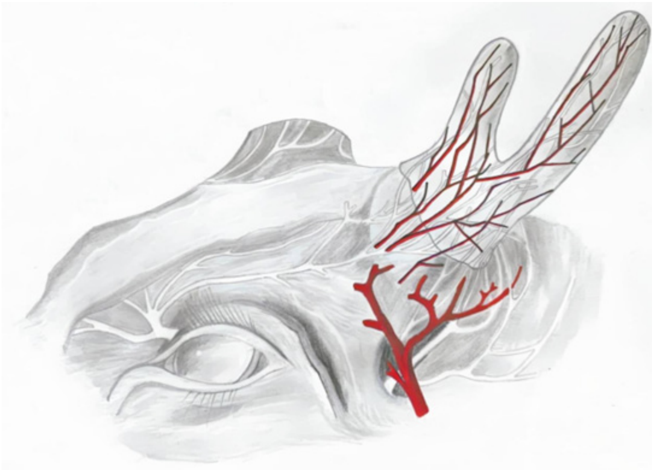

Figure 2: Nerve origin of deer antler. The nerves of deer antler originate from the temporal and supraorbital branches of the trigeminal nerve, and they accompany the superficial temporal artery to the deer antler [3].

Nerve regeneration mechanisms

Nerve regeneration in deer antlers is a complex process involving chemical and mechanical factors [11]. Chemical induction is mediated by secretion of neurotrophic and angiogenic factors by stem cells and other cells [12,13]. Mechanical tension, generated by the rapid growth of the antler, also plays a significant role in promoting nerve elongation. Studies have shown that axons can grow at a remarkable rate under mechanical tension, which is significantly faster than their intrinsic growth rate [11].

Chemical induction: Neurotrophic factors, including nerve growth factor, neurotrophin-3, and brain-derived neurotrophic factor, are highly expressed in regenerating antlers, and they play crucial roles in promoting nerve survival, differentiation, and outgrowth [12-14]. Additionally, growth factors including insulin-like growth factor-1 and fibroblast growth factor-2 contribute to nerve regeneration by stimulating cell proliferation and angiogenesis [11,15].

Mechanical induction: The rapid growth of deer antlers generates mechanical tension that promotes elongation of the nerves [11]. Studies have demonstrated that axons can grow at a rate of up to 8 mm/day under mechanical tension, which is significantly faster than their intrinsic growth rate. Mechanical induction is postulated to be a key factor in the remarkable regenerative capacity of deer antler nerves.

Types of antler stem cells (AnSCs)

The renewal of antlers relies on the proliferation and differentiation of antler stem cells (AnSCs). Their descendant cells can sustain the complete annual regeneration of antlers, and the cells stemming from these descendants can propel the antler to grow at an astonishing rate (up to 2 cm/d) [16]. AnSCs can be one of three types [6]: (1) Antlerogenic periosteum cells (for initial pedicle and first antler formation); (2) pedicle periosteum cells (for annual antler regeneration); and (3) Reserve Mesenchyme Cells (RMCs) (for rapid antler growth). Previous studies have demonstrated that AnSCs can be classic Mesenchymal Stem Cells (MSCs) or Embryonic Stem Cells (ESCs), and they can differentiate into multiple cell types, *in vitro*. Thus, AnSCs are defined as MSCs with partial ESC attributes.

The pedicle and antlers have internal (cartilage and bone) and external (skin, blood vessels, and nerves) structural components [16,17]. Deer are not born with pedicles; they develop from the frontal crests as they approach puberty. Pedicles and first antlers (Figure 3B) are initially formed from the frontal crest periosteum, termed the Antlerogenic Periosteum (AP). Removal of the AP prevents formation of the pedicle and first antler, and transplantation of an AP into a deer can induce the formation of an ectopic antler. Morphological and histological studies have shown that the growth center of regenerating antlers (Figure 3C) is initially formed by the proliferation and differentiation of pedicle periosteum cells. The growth center of the antler (Figure 3D) is located at the tips. The rapid growth of antlers is mainly achieved through the activity of cells in the proliferation zone, *i.e.*, the reserve mesenchyme. Therefore, reserve mesenchyme cells must have substantial potential for proliferation to sustain such a formidable growth rate (Figure 3).

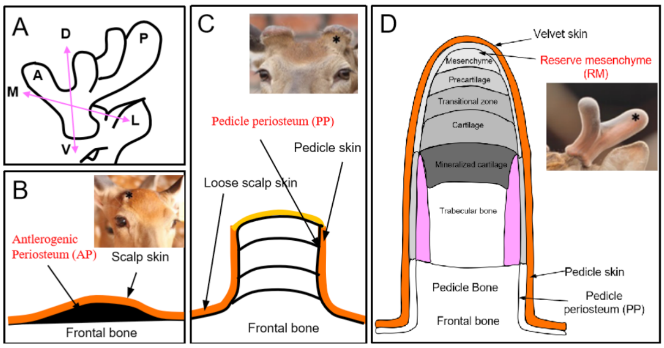

Figure 3: Schematic diagrams of the anatomical locations of antler stem cells. A: The three axes of antler development: A ↔ P: Anterior-posterior axis; D ↔ V: Dorso-ventral axis; M ↔ L: Mediolateral axis; B: The antlerogenic periosteum is present in the embryo, and after birth as a localized thickening of the periosteum of the frontal bone; C: Regeneration of an antler is initiated from the cells in the pedicle periosteum; D: There is endochondral bone growth at the distal tip, and cells in the reserve mesenchyme are responsible for rapid antler growth [16]. Copyright © The author(s). Published by Baishideng Publishing Group Inc. Stars (*) in the insert figure: Location of antler stem cells.

Conclusion and future directions

Deer antlers are a unique and valuable model for studying neurogenesis and nerve regeneration. The remarkable regenerative capacity of antler nerves, mediated by stem cells and various growth factors, provides insights into the fundamental biology of tissue regeneration. Future studies should focus on elucidating the precise molecular pathways involved in nerve regeneration, and on identifying the key factors that regulate stem cell differentiation and function. In addition, the development of safe and effective cell-based therapies for nerve injury repair requires rigorous pre-clinical and clinical testing.

In conclusion, the study of neurogenesis in deer antlers offers exciting prospects for advancing understanding of tissue regeneration, and for developing novel therapies for the treatment of human diseases. Future studies in this area have the potential to provide breakthroughs in regenerative medicine and to improve the quality of life of patients with nerve injuries and age-related degenerative conditions.

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