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Editorial

Stem Cells, Stem Cell Niche and Mammalian organ Regeneration -Insights from Studying Deer Antler Biology

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Editorial

Organ regeneration is the "Holy Grail" of modern regenerative medicine. To realize this dream, regenerative medicine must be underpinned by regenerative biology, which seeks to understand the mechanism of regeneration through investigation of different model systems. Among these systems, deer antler stands out as the only mammalian appendage capable of complete renewal (Figure 1). Therefore, it offers a unique opportunity to explore how nature has solved the problem of regeneration of a complex mammalian organ including tissues of bone, cartilage, blood vessels, nerves and full thickness of skin.

Research finds that antler regeneration relies on the presence of the periosteum of a pedicle, from which an antler casts and fully regenerates. Deletion of the Pedicle Periosteum (PP) abrogates future antler regeneration. This unique feature of the PP has been attributed to its developmental origin, i.e. it is directly differentiated from Antlerogenic Periosteum (AP). The AP is a piece of periosteum that overlies a frontal crest of a pre-pubertal deer before the initiation of pedicle growth but it disappears when a pedicle starts to develop. Removal of the AP abolishes the future growth of a pedicle and an antler. However, transplantation of the AP elsewhere on the deer body induces ectopic pedicle and antler formation. Interestingly, cells from both the AP and the PP express key embryonic stem cell markers, such as Oct4, Nanog and SOX2 (Figure 2) and can be induced to differentiate into multiple cell lineages such as cartilage, bone, fat, muscle and nerves (Figure 3). Therefore, the AP and the PP cells are called antler stem cells, with the former destined for antler generation and the later for antler regeneration.

Being called stem cells, the AP and the PP cells must be located in their special niches. Histological experiments revealed that to launch antler generation and regeneration, the AP and the PP must become intimately associated with their enveloping skin respectively, indicating that these stem cells must interacts with the skin to gain the potential to generate or regenerate antlers. Study with membrane insertion showed that antler generation or regeneration cannot occur if these two interactive tissue types are interposed by an impermeable membrane at the stage prior to becoming closely attached to each other. In contrast, if the interposition occurs at the stage after they become closely attached to each other, the antler generation and regeneration would still be able to initiate. Interestingly, insertion of a semi-permeable membrane (0.45 μm pore size) is unable to block the interactions between these two tissue types. Overall, the closely attached skin has been shown to be the niche for antler stem cells, and the nature of these interactions between the antler stem cells and the niche is only transient and mediated by diffusible molecules.

Ectopic transplantation of the AP reveals that only the skin that adorns hair follicles is capable of interaction with the AP to initiate antler formation. Further research pinpoints out that it is the dermal papilla cells that mediate the interactions between the tissue derived from the AP and the epidermis of the skin, and only the cellular layer cells (opposed to the fibrous layer cells) of the AP that participate in such interactions with the skin. Based on these findings, we have put all the interactive cell types together in a culture vessel and established a 3D co-culture system. This system can minimize the aggregates of the dermal papilla cells compared to the singular cultured counterparts, and hence can effectively mimic the true *in vivo* situation. Consequently, we have successfully built up an effective in vitro platform for the isolation of the putative interactive small molecules. The eventual identification of these molecules would not only greatly enhance our knowledge of stem cell-based mammalian organ regeneration, but also have significant impacts on regenerative medicine in general.

Figure 1: Annual antler growth cycle. In spring, hard antlers drop off from the pedicles, and antler regeneration immediately follows. Rapid antler growth occurs in summer. Growing antlers are enveloped with velvet skin. In autumn, antlers become fully calcified and velvet skin starts to shed. In winter, hard antlers are attached to their pedicles and subsequently cast in the next spring, which triggers a new round of antler regeneration.

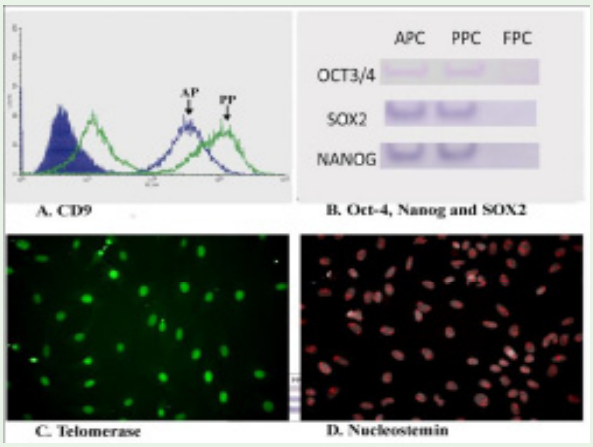

Figure 2: Figure 2: Cell markers and genes associated with embryonic self-renewal and pluripotency in antler stem cell populations. A. Cell surface expression of the embryonic stem cell marker CD9 in the AP (blue trace) and PP (green trace) cell populations.

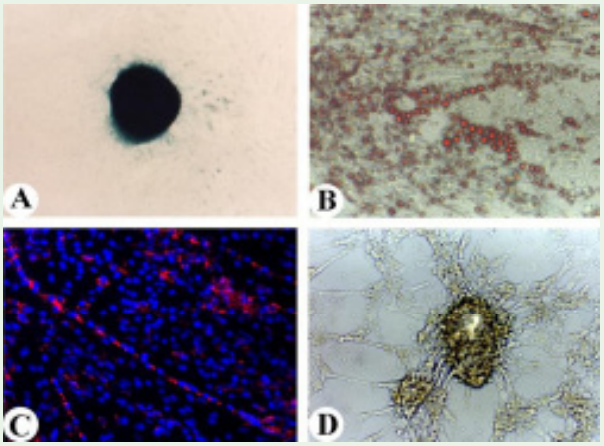

Figure 3: Multipotency of antler stem cells in vitro. A. Cartilage nodule (blue) formed by the PP cells in a micro mass culture.B. Adipocytes differentiated from the PP cells in the culture medium containing linoleic acid.C. Myotube formed from AP cells (red color, labeled with fluorescent dye DiI) when co-cultured with C2C12 cells.D. Neuronal-like cells differentiated from the PP cells when cultured in N2 medium. Notice the extended neuritis from each cell body.