Comparative RNA-Seq Analysis of Fibroblast-Mediated Regeneration and Fibrosis in *Rangifer tarandus*

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Abstract

Regenerative healing is a rare phenomenon in adult mammals, with reindeer antlers serving as one of the most well-studied models of complete tissue regeneration. Unlike most tissues, which heal through fibrotic repair and scar formation, reindeer antlers regenerate fully, restoring both structure and function without scarring. In this study, I investigate the molecular mechanisms underlying the regenerative healing of reindeer antlers by comparing gene expression profiles in antler velvet (regenerating tissue) and dorsal skin (fibrotic repair) across four time points: Day 0, Day 3, Day 7, and Day 14 post-injury [4].

The transcriptomic dataset was generated by the Biernaskie Lab at the University of Calgary, Department of Comparative Biology and Experimental Medicine, and comprises bulk RNA-seq data from wounded and control tissues of antler velvet and dorsal skin [3]. The dataset includes 34 samples collected from 4 individual reindeer, spanning four post-injury timepoints (Day 0, 3, 7, and 14), with both tissue types represented at each timepoint. I performed a time-course bulk RNA-seq analysis, utilizing DESeq2 for differential gene expression analysis. Protein sequences for the significantly regulated genes were retrieved from Ensembl BioMart, followed by functional annotation using InterProScan [1]. Gene Ontology (GO) terms were enriched and categorized into regenerative, fibrotic, or other biological processes to distinguish the pathways activated in these two distinct tissue healing modes.

My results show that antler velvet tissue activates a unique combination of regeneration-related genes, including those involved in keratin production, ion channel activity, and neural signaling at Day 14, a time point critical for tissue functional restoration. These findings suggest that neuronal regeneration, epithelial growth, and vascular remodeling are key components of the regenerative process. In contrast, dorsal skin healing is characterized by persistent expression of fibrosis-related genes, such as collagen crosslinking and extracellular matrix production, which are associated with scar formation and tissue stiffening. Inflammatory signaling remains prominent throughout the skin healing process, with little to no activation of regeneration-related pathways. The analysis pipeline and findings are accessible at [https://github.com/mickeysan-git/Rangifer-tarandus].

Clear Statement of Research Question

My research aims to investigate how temporal gene expression dynamics distinguish regenerative healing in reindeer antlers from fibrotic repair in dorsal skin across four time points: Days 0, 3, 7, and 14 post-injury. The study focuses on understanding the molecular pathways activated during these distinct healing processes by comparing gene expression profiles in regenerating and fibrotic tissues. A key objective is to identify the genes and biological processes that drive regeneration and how these pathways differ from those associated with fibrosis. Additionally, the research explores how gene expression progresses over time, contributing to functional tissue restoration in antler velvet versus scar formation in dorsal skin. By addressing these questions, the study provides a comprehensive comparison of the molecular mechanisms of regenerative and fibrotic healing, with potential implications for therapeutic strategies aimed at promoting regeneration in fibrotic tissues.

Hypothesis

I hypothesize that regenerative healing in reindeer antlers involves the activation of distinct molecular pathways that promote tissue regrowth, including early immune resolution and subsequent activation of tissue-specific repair mechanisms. In contrast, fibrotic healing in dorsal skin is driven by persistent immune signaling and excessive extracellular matrix deposition, leading to scar formation. I expect to see temporal differences in gene expression between the two tissues, with antler velvet showing a shift toward functional tissue restoration by Day 14, while dorsal skin continues to exhibit markers of fibrosis and inflammation.

Furthermore, similar regenerative patterns have been observed in other animals, such as axolotls and zebrafish, which are known for their remarkable regenerative abilities, including limb regeneration and heart tissue recovery [2]. Given that we see this regenerative pattern in other species, I expect to see similar behavior in reindeer antlers.

Sufficient Background for Non-Expert Reader

Wound healing is a complex biological process that occurs in response to tissue injury. In most adult mammals, this process typically follows a fibrotic healing pathway, which involves the formation of scar tissue. The body responds to injury by activating fibroblasts, cells responsible for producing extracellular matrix (ECM), which includes collagen. While scar tissue helps to close the wound and restore the skin's surface, it does not fully restore the tissue's original structure or function. Scar tissue is typically thicker, stiffer, and non-functional, leading to a loss of tissue flexibility and, in many cases, permanent dysfunction [5].

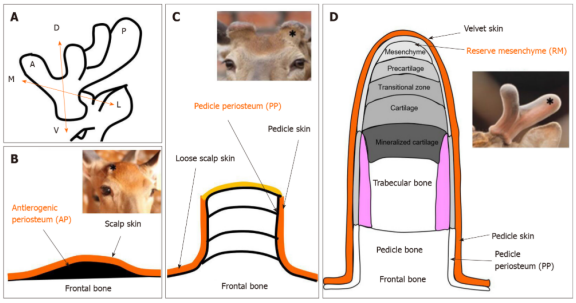

Figure 1: Schematic Diagram of Antler Stem Cell Locations

Unlike the typical fibrotic healing observed in most mammalian tissues, reindeer antlers are an exceptional example of regenerative healing, a process in which the tissue regenerates fully, restoring both structure and function without scarring. This ability is unique among adult mammals. Antlers grow and shed annually, with new antler growth starting from a small nub that gradually becomes larger and more complex. When antlers are injured, they heal rapidly and without the formation of scar tissue, re-establishing the full tissue architecture. Regenerative healing in antlers involves a well-coordinated sequence of events, including immune resolution, stem cell activation, and functional restoration of nerves, blood vessels, and epithelial tissue (Figure 1). Unlike the typical fibrotic response, the healing tissue undergoes remodeling that leads to the functional restoration of the antler's complex structure [4].

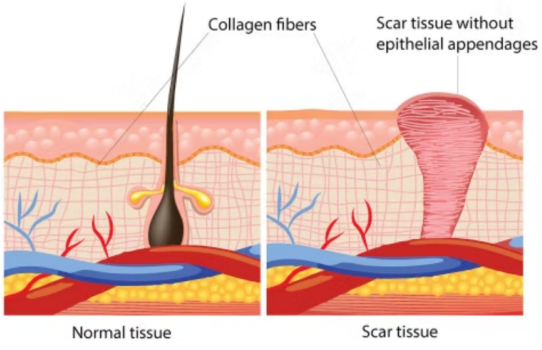

Figure 2: Normal Tissue versus Scar Tissue

In contrast, dorsal skin (the back skin of reindeer) heals through the typical fibrotic repair process seen in most mammals. When skin is injured, the body's initial response is to stop the bleeding and form a protective clot. Over time, the immune system activates inflammatory cells and fibroblasts, which deposit collagen and other ECM components to close the wound [5]. However, the resulting tissue lacks the flexibility and functional properties of the original skin. This is because the fibroblasts in fibrotic healing produce an excessive amount of collagen, creating a stiff, fibrous scar instead of regenerating the tissue (Figure 2). Additionally, the inflammatory response continues longer than in regenerative healing, preventing the skin from fully restoring its original function.

Regenerative healing is rare in adult mammals due to several evolutionary and biological constraints. In many species, regeneration is a trait seen primarily during early development or in specific tissues (e.g., liver regeneration in some mammals or limb regeneration in certain amphibians). Evolutionarily, mammals have developed robust fibrotic repair mechanisms that are effective at closing wounds quickly and preventing infection [6]. However, these processes are often at odds with the capacity for complete regeneration, as the biological mechanisms required for regeneration, such as stem cell activation and neurogenesis, are often suppressed or not fully activated in adult tissues. This makes the regenerative capacity of reindeer antlers a unique and valuable model for understanding how adult tissues might be induced to regenerate fully, without fibrosis, offering a potential pathway for therapeutic advances in regenerative medicine.

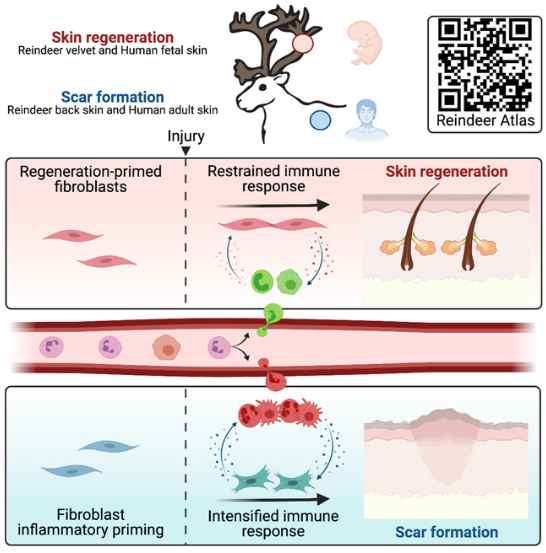

Figure 3: Reindeer Healing Comparison

By studying both antler and dorsal skin healing within the same organism, researchers can directly compare regenerative and fibrotic processes in a controlled biological context. This side-by-side analysis enables the identification of key genes, signaling pathways, and cellular behaviors that differ-

entiate scar-free regeneration from scar-forming repair (Figure 3). Such comparisons are especially powerful because they remove inter-species variability, highlighting tissue-specific responses rather than systemic differences [4].

Motivation for Problem Addressed

Most mammals, including humans, typically heal via fibrosis, which leads to the formation of scar tissue and often results in permanent loss of tissue function. Given the clinical significance of scar formation and the long-term consequences it has on tissue function, understanding the regenerative processes in reindeer antlers could have important implications for treating human diseases. These diseases, such as fibrotic disorders of the heart, lungs, and liver, or chronic wounds, often result in irreversible tissue damage. By studying how reindeer antlers heal without scarring, we may unlock potential therapeutic strategies to promote regeneration in human tissues instead of fibrosis.

Additionally, although species like axolotls and zebrafish are known for their regenerative abilities, the mechanisms underlying mammalian regeneration remain poorly understood [2]. By studying reindeer, which are mammals with regenerative healing capabilities, we can expand our understanding of how these processes work in larger, more complex organisms. This research could help bridge the gap between the regenerative abilities of smaller animals and the challenges mammals face in achieving similar healing.

The insights gained from this study could contribute to advancing regenerative medicine. The ultimate goal is to identify the specific genes, pathways, and signaling networks involved in regeneration, which could lead to the development of therapies that promote tissue regeneration in humans. This could significantly improve the treatment of injuries, diseases, and conditions that currently lead to scar tissue formation, offering hope for patients suffering from fibrosis-related complications.

Presentation of Results

Presentation of Results Day 0

At Day 0 post-injury, the volcano plot shows broad transcriptional changes between antler velvet and dorsal skin, with 57 differentially expressed genes (Figure 4). Notable up-regulated genes in velvet tissue include *COL12A1*, *CDH11*, and *MMP13*, while *SCARA5*, *HOXC8*, and *HP* are repressed. This reflects an early and tissue-specific transcriptional response to injury.

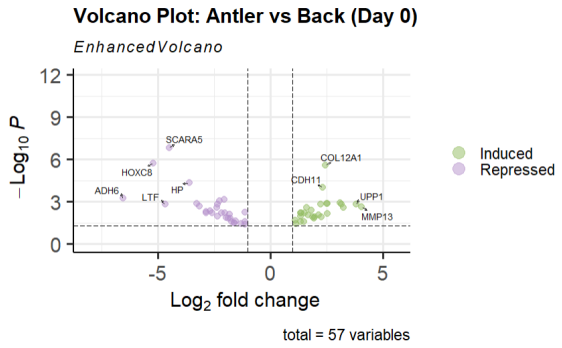

Figure 4: Day 0 Volcano Plot

GO enrichment identifies major biological processes related to *protein binding*, *membrane* components, *calcium ion binding*, *keratin filament organization*, and *DNA-templated transcription* (Figure 5). These processes suggest the tissue is engaged in wound closure, signaling, and scaffolding construction.

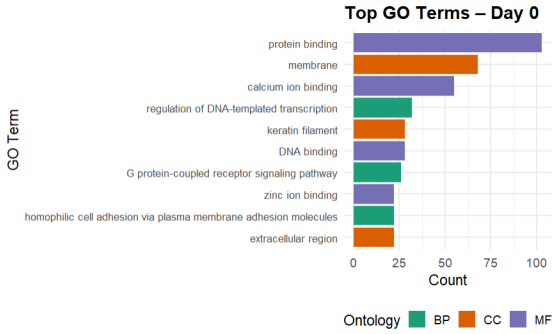

Figure 5: Top 10 GO Terms, Day 0

InterProScan annotations reveal dominant protein families associated with tissue repair: Type II keratin, fibronectin type III, estrogen receptor, chemokine receptor, and cadherin signatures (Figure 6). These protein domains are foundational to epithelial stability, immune guidance, and extracellular matrix (ECM) assembly.

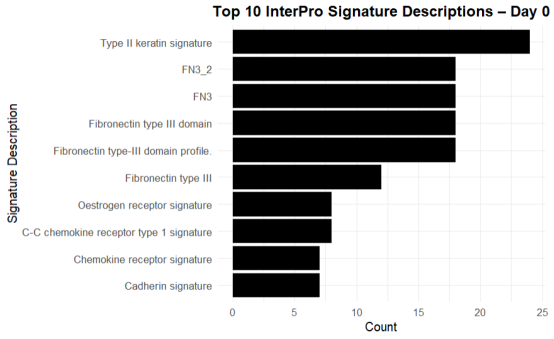

Figure 6: Top 10 InterPro Descriptions, Day 0

Regeneration-related terms further confirm this activation. Immune recruitment is evident with GO terms such as *positive regulation of monocyte chemotaxis*, *macrophage chemotaxis*, and *neutrophil chemotaxis*. Structural rebuilding is supported by terms like *cell morphogenesis*, *cell migration*, and *endothelial cell migration*. Importantly, *axon regeneration* and *neural regeneration related proteins* appear at this early stage, indicating the initiation of neural recovery pathways alongside epithelial repair.

Presentation of Results Day 3

At Day 3 post-injury, gene expression differences between antler velvet and dorsal skin narrow, with 22 differentially expressed genes detected (Figure 7). Notable up-regulated genes in velvet tissue include *GRK7* and *CEP112*, while *MAGEL2*, *PTH2R*, and *OTOP3* are repressed.

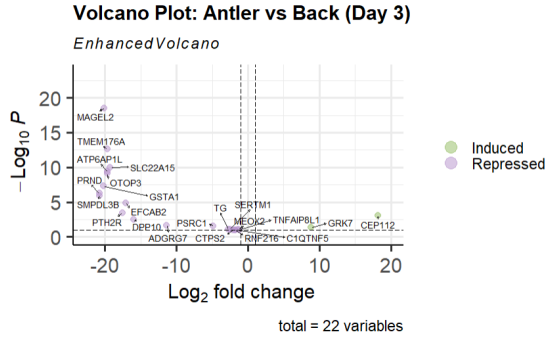

Figure 7: Day 3 Volcano Plot

GO enrichment highlights key biological processes involved in signal regulation, such as *G protein-coupled receptor activity*, *protein phosphorylation*, *ATP binding*, and *DNA binding* (Figure 8). These results suggest an early shift from injury response to regulatory signaling and transcriptional control.

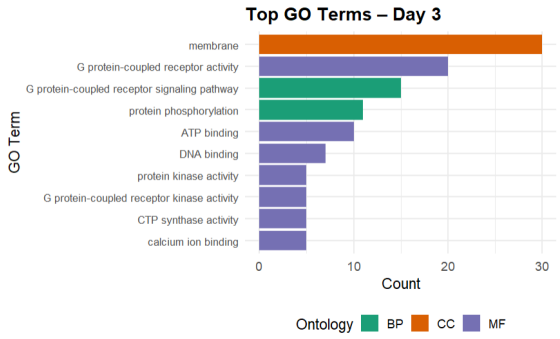

Figure 8: Top 10 GO Terms, Day 3

InterProScan analysis shows an enrichment of protein domains involved in developmental signaling and transcriptional coordination, including Secretin-like GPCR superfamily, GPCR kinase, and Homeobox signatures (Figure 9). Additional hits include EF-hand calcium-binding motifs and hormone receptor domains.

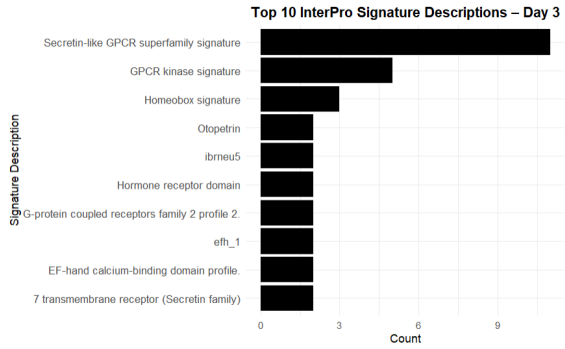

Figure 9: Top 10 InterPro Descriptions, Day 3

While no specific regeneration-related GO terms were strongly enriched at Day 3, the data suggest a transitional phase between early structural repair and later functional regeneration. Compared to Day 0, relatively few genes are differentially expressed, and the overall biological activity appears more subdued. This may reflect a temporary stabilization period, during which early immune and epithelial responses begin to resolve and the tissue shifts toward regulatory coordination.

Presentation of Results Day 7

By Day 7, transcriptional divergence increases again with 92 differentially expressed genes between antler velvet and dorsal skin (Figure 10). up-regulated genes in velvet tissue include *LATS1*, *ZNF389*, *HEPH*, and *OTOP3*, while repressed genes include *KRT9*, *FGF5*, and *PRRG4*.

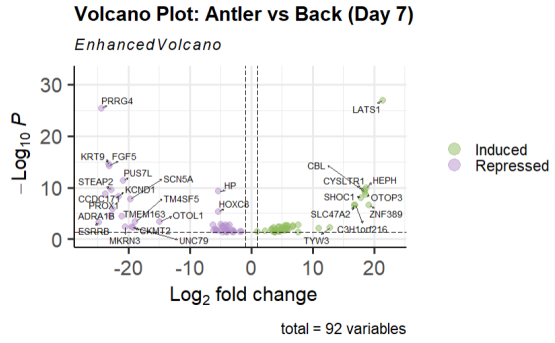

Figure 10: Day 7 Volcano Plot

GO enrichment reveals a strong emphasis on *membrane*-associated processes, *G protein-coupled receptor signaling*, *potassium ion transport*, and *voltage-gated channel activity* (Figure 11). These terms reflect tissue remodeling, ionic control, and emerging functional specialization.

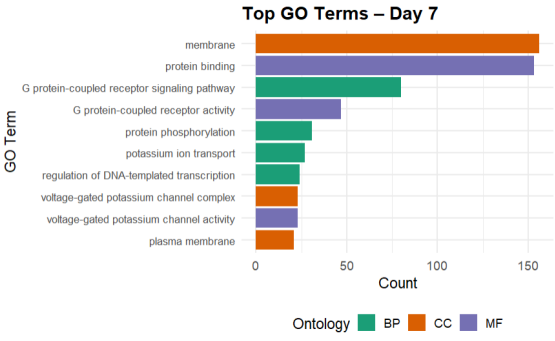

Figure 11: Top 10 GO Terms, Day 7

InterProScan results show top hits including Rhodopsin-like GPCRs, Type II keratin, Shal and Kv4.1 potassium channels, thrombin and angiotensin receptors, and TPR domains (Figure 12). These reflect both structural components and sensory/vascular signaling integration.

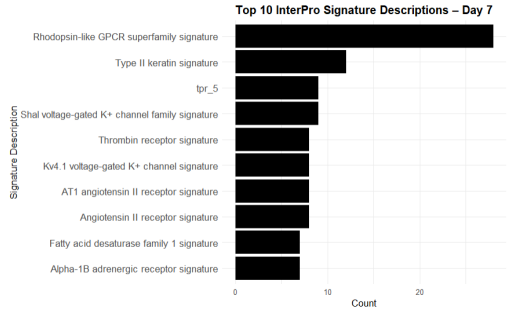

Figure 12: Top 10 InterPro Descriptions, Day 7

Regeneration-related terms detected include *dendritic spine morphogenesis*, *axon regeneration*, *positive regulation of epithelial cell differentiation*, and *tissue regeneration*. These indicate that antler velvet has begun active integration of neuronal and epithelial pathways, further distinguishing its regenerative progression from fibrotic repair.

Presentation of Results Day 14

At Day 14, the number of differentially expressed genes drops to 34, indicating a late-stage stabilization of gene expression profiles between antler velvet and dorsal skin (Figure 13). up-regulated genes in velvet include *SLC38A1*, *OTOP3*, *GLIPR1*, and *F5*, while repressed genes include *HOXC8*, *CACNA2D3*, and *SCN5A*.

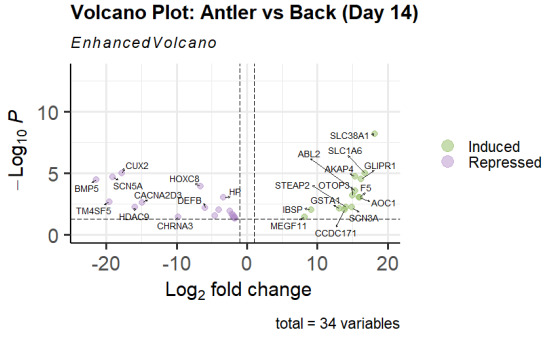

Figure 13: Day 14 Volcano Plot

GO enrichment identifies functional categories involved in *membrane* association, *voltage-gated sodium channel activity*, *structural molecule activity*, and *ion transport* (Figure 14). These categories suggest terminal tissue remodeling and restored excitability in velvet tissue.

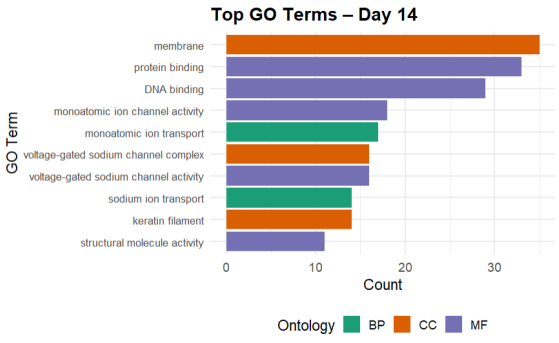

Figure 14: Top 10 GO Terms, Day 14

InterProScan results reveal late-stage enrichment in domains such as Type I and II keratin, TPR repeat motifs, voltage-gated Na^+ channels, tyrosine kinase catalytic domains, and neurotransmitter-gated ion channels (Figure 15). These signatures support both structural integrity and neural signaling restoration.

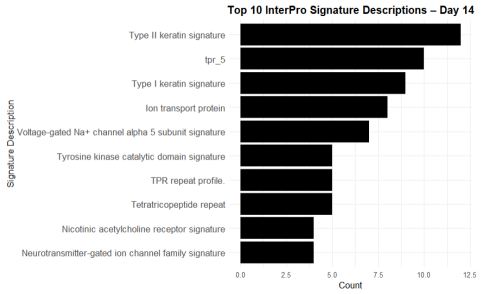

Figure 15: Top 10 InterPro Descriptions, Day 14

Although the only regeneration-related GO term explicitly flagged at Day 14 is *epithelial cell differentiation*, the broader GO enrichment and InterProScan results suggest that regeneration has entered its final phase. In total, these point to the completion of the regeneration process, with both structural and functional restoration achieved in antler velvet by Day 14.

Analysis Across All Timepoints

To compare gene expression dynamics across the full regeneration timeline, two summary-level analyses were performed. First, GO term enrichment across all days highlights consistently up-regulated processes related to epithelial recovery, including *epidermis development*, *keratinization*, and *tissue development* (Figure 16). These categories appear throughout the time course, indicating a persistent structural repair program.

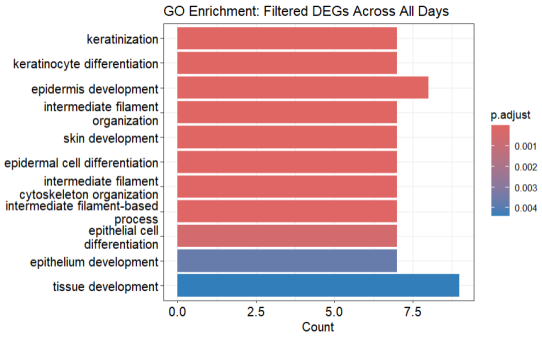

Figure 16: GO Enrichment for DEGs Across All Days

A just-in-time comparison between Day 0 and Day 14 shows a shift in GO term activation over time (Figure 17). Day 0 is enriched for structural and developmental terms, while Day 14 is dominated by transport and neural signaling processes such as *membrane depolarization*, *ion transport*, and *neural action potential*.

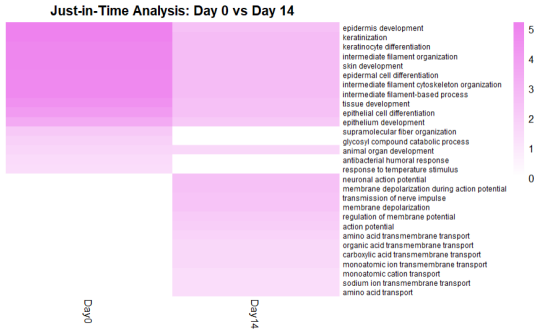

Figure 17: Just-in-Time Heatmap: Day 0 vs Day 14

Together, these results highlight a clear temporal progression from epithelial repair to functional integration over the course of regeneration.

Interpretation of Results

Immediately after injury, antler velvet activates a robust and coordinated response. The tissue prioritizes sealing the wound, rebuilding the epithelial barrier, and reestablishing structural integrity. Structural proteins like Type II keratin and fibronectin type III domains form the foundation of epithelial recovery. Keratins create intermediate filaments that provide tensile strength to regenerating tissue, while fibronectin offers a temporary matrix that supports keratinocyte migration, fibroblast adhesion, and the organization of newly deposited collagen. The up-regulation of cadherin domains indicates early re-establishment of cell–cell junctions, essential for re-forming layered epithelial structures.

Alongside structural rebuilding, estrogen receptor signatures appear prominently. These are known to accelerate keratinocyte proliferation, angiogenesis, and fibroblast activation while suppressing prolonged inflammation, pointing to an environment that promotes quick repair without excessive scarring. Immune activity is strongly represented through chemokine receptor domains, which mediate the recruitment of monocytes, neutrophils, and macrophages. This aligns with the detection of multiple chemotaxis-related GO terms, including positive regulation of monocyte chemotaxis, neutrophil chemotaxis, and macrophage chemotaxis.

Crucially, regeneration-specific processes are already underway. Axon regeneration, neural regeneration-related proteins, and cell morphogenesis terms indicate that velvet tissue initiates neural repair alongside epithelial barrier formation. Rather than waiting for structural healing to complete, reindeer velvet appears to engage sensory and functional recovery from the very beginning.

By Day 3, the number of differentially expressed genes decreases, signaling a shift in biological priorities. While overt structural and immune activities become less prominent, this stage is marked by the activation of key regulatory and sensory programs that help coordinate regeneration. Multiple G-protein–coupled receptor (GPCR) superfamilies and GPCR kinase domains are detected, which

collectively govern how cells perceive and respond to hormones, chemokines, and growth factors.

Importantly, homeobox transcription factors emerge at this stage. These proteins are essential for body patterning and morphogenesis, and their expression suggests that cells are beginning to organize into spatially patterned structures. The appearance of EF-hand calcium-binding motifs further supports this view. Calcium signaling is central to wound healing, regulating the migration of keratinocytes, secretion of extracellular matrix, and activation of repair pathways.

Although no regeneration-specific GO terms are directly flagged at Day 3, the presence of these signaling and patterning pathways implies a strategic pause in which the tissue shifts away from immediate repair and toward internal recalibration. This sets the stage for more specialized rebuilding in the following days.

On Day 7, the regenerative process re-accelerates, marked by the up-regulation of genes associated with membrane organization, epithelial polarity, and neural activity. Structural support continues through Type II keratin signatures, while tetratricopeptide repeat (TPR) domains help stabilize protein complexes required for cell migration and scaffold assembly. These elements suggest that cells are not only proliferating but also organizing into functional layers. Multiple potassium channel proteins, including Shal (Kv4.1) and voltage-gated ion channels, emerge. These channels are essential for re-establishing membrane potential, a prerequisite for neural signaling. The up-regulation of rhodopsin-like GPCRs and thrombin receptors further supports vascular remodeling and cell–cell communication.

Biological processes such as axon regeneration, dendritic spine morphogenesis, and epithelial cell differentiation are prominently represented. The tissue is actively forming complex neural and epithelial structures, not merely replacing lost components. Signals linked to B cell proliferation suggest that the immune system has shifted into a supportive role, helping maintain a regenerative environment rather than driving inflammation.. This stage reflects a critical transition from raw repair to functional tissue formation.

By Day 14, transcriptional activity becomes more refined, but the genes that remain highly expressed are associated with excitability, neural responsiveness, and broader physiological readiness. Structural stabilization is completed through the co-expression of Type I and Type II keratins, which form fully mature epithelial cytoskeletons.

Most notably, electrical and sensory readiness dominate the biological profile. Voltage-gated sodium channel alpha subunits, neurotransmitter-gated ion channels, and nicotinic acetylcholine receptors are all active, indicating that neural circuits are reconnecting and that the tissue is capable of responding to neural input. This mirrors the GO enrichment in membrane depolarization, ion transport, and action potential transmission, indicating not only re-innervation but also the full restoration of electrical signaling.

Although only epithelial cell differentiation remains flagged as a regeneration-associated term at this point, the surrounding molecular environment strongly supports the interpretation that full functional recovery has occurred. The healing process has transitioned from repair to reintegration, resulting in structurally complete and responsive tissue.

Conclusion

This study highlights the unique regenerative capacity of reindeer antler velvet, which progresses through a clearly defined series of biological phases. From early immune recruitment and epithelial repair to later stages of tissue remodeling and neural reintegration, the process is both rapid and highly organized. Each stage brings new biological priorities, first sealing and stabilizing the wound, then coordinating internal signaling, and ultimately rebuilding a fully functional tissue system. By Day 14, the regenerated velvet displays hallmarks of mature, responsive tissue, including restored electrical signaling and structural differentiation.

These findings directly support the initial hypothesis that antler velvet regeneration is driven by distinct molecular programs involving early immune resolution and the timely activation of tissue-specific repair mechanisms. In contrast to dorsal skin, which is characterized by persistent inflammation and fibrotic signaling, velvet tissue transitions efficiently toward functional recovery. This was reflected in the temporal gene expression patterns observed, with antler velvet showing a clear shift toward neural activity and epithelial maturation by the final timepoint.

Unlike the scar-driven healing seen in most mammalian tissues, antler velvet regeneration achieves both architectural and physiological restoration. Together, these results not only provide new insight into how regeneration unfolds in a complex mammalian system but also offer a valuable framework for identifying the timing and molecular conditions necessary to support true tissue regeneration in other contexts, including human medicine.

Discussion of Limitations

Several limitations should be considered when interpreting the findings of this study. First, gene expression was measured using bulk RNA sequencing, capturing average transcriptional activity across all cell types within each tissue sample. Because antler velvet contains a mix of epithelial, immune, stromal, and neural cells, this approach does not resolve which cell types are contributing to specific changes over time. Signals associated with neural signaling, immune modulation, or epithelial remodeling cannot be precisely linked to individual cell populations.

Second, the sample design included tissues from four individual animals, two tissue types (antler velvet and dorsal skin), and four timepoints. While this design allowed for broad comparisons across regenerative and fibrotic contexts, sample size and tissue complexity limit the ability to distinguish individual variability or subtle cell-state transitions. Additionally, one sample from the antler Day 14 group and one from the back Day 14 group were not available for sequencing, further reducing replication at the final timepoint. Moreover, antler velvet and dorsal skin differ not just in healing outcome, but also in baseline structure and function. Some differences in gene expression may reflect these intrinsic tissue properties rather than their response to injury alone.

In addition, all gene annotations were based on *Bos taurus* (cow) reference databases, which were used as a proxy for *Rangifer tarandus* due to limited species-specific annotations. While reindeer and cattle are closely related, important species- or tissue-specific features may be misclassified or overlooked. This is especially relevant for genes involved in antler-specific processes, neural regrowth, or seasonal tissue adaptation. For example, several late-stage signaling genes were not tagged as regeneration-related, despite supporting neural reintegration, likely reflecting annotation gaps rather than biological absence.

Clear Statement of Future work

In this study, gene function and pathway analysis were based on annotations from the *Bos taurus* (cow) genome due to limited reference data for *Rangifer tarandus*. To address this, I attempted to build a draft gene annotation resource for reindeer by compiling available protein, gene, GO, and chromosomal information across multiple databases. The code used to generate this preliminary reference is available in the GitHub repository linked in the Abstract section. However, the resulting annotations were incomplete and lacked the coverage needed to fully replace the established *Bos taurus* framework. Building a more comprehensive and validated gene annotation database for *Rangifer tarandus* remains a critical next step for improving functional accuracy in future analyses.

Performing a cross-species analysis can offer another opportunity for insight on what genes and biological processes drive regeneration. Identifying conserved genes or pathways between reindeer antler regeneration and other regenerative models, such as axolotls, zebrafish, or digit tip regeneration in mice, could help reveal core components of mammalian regeneration. These comparisons would also help distinguish regeneration-specific programs from general wound healing or species-specific traits.

Finally, future work could explore whether the transcriptional patterns identified here are consistent at the single-cell level. Integration with existing single-cell datasets, or the generation of new single-cell data from antler velvet, would allow for the resolution of which cell types are driving each stage of regeneration. This could clarify whether neural, immune, or epithelial signals observed in the bulk data arise from distinct populations or shared regulatory programs.

Together, these approaches would help refine and extend the findings of this study, improving both the accuracy and interpretability of regeneration-related transcriptional dynamics in this unique mammalian system.

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