Exploring the Single-Cell Transcriptome Landscape of the Human Dorsal Root Ganglion in Diabetic Peripheral Neuropathy

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INTRODUCTION

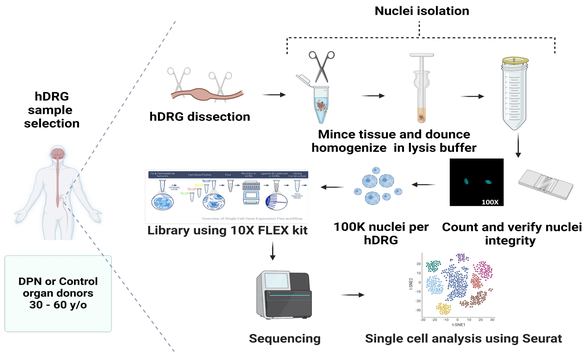
Diabetic Peripheral Neuropathy (DPN) is a prevalent and clinically significant complication of diabetes. This neuropathy encompasses a wide spectrum of clinical pathologies associated with peripheral nervous system dysfunction. It is characterized by nerve conduction impairment, dieback of nerve endings from the skin, spontaneous pain, and numbness in extremities which poses substantial challenges in management and treatment. Despite its widespread impact, the precise etiology of diabetic peripheral neuropathy remains elusive.

In this study, we conducted single-nucleus RNA sequencing on human dorsal root ganglion (DRG) tissues recovered from organ donors with a documented history of diabetes and neuropathic pain. Our primary objectives encompassed elucidating distinct populations of neurons and comprehending their transcriptomic variations between healthy and DPN DRGs.

https://genesismedwa.com/blog-diabetic-neuropathy/

METHODS

Single nuclei RNA Sequencing from hDRGs



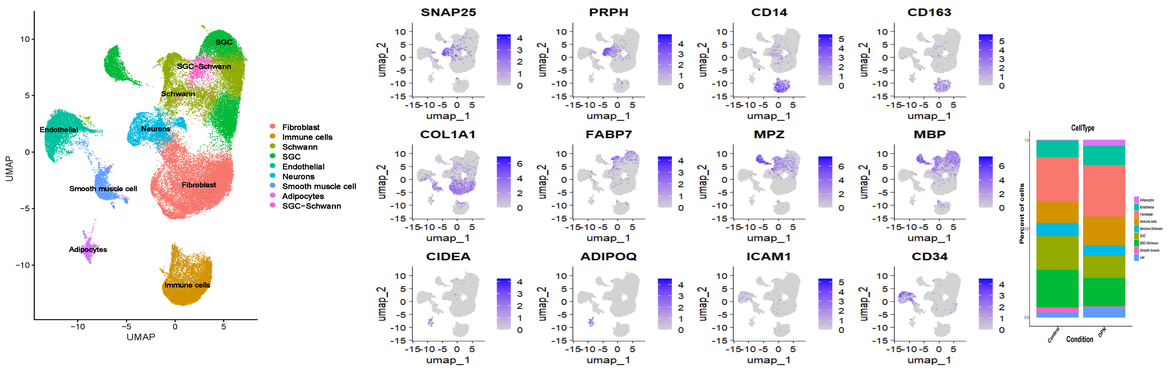
Quality control metrics with ambient RNA cleanup

Average # nuclei/sample	Total # nuclei	Total # nuclei after SoupX	Median reads per nuclei	Median genes per nuclei	Total genes detected	Mean reads per nuclei
6,395.13	51,161.00	~58,549	4,030.25	1,311.63	18066	11,392.00

4 DPN and 4 control hDRGs, 2 females and 2 males in each group.

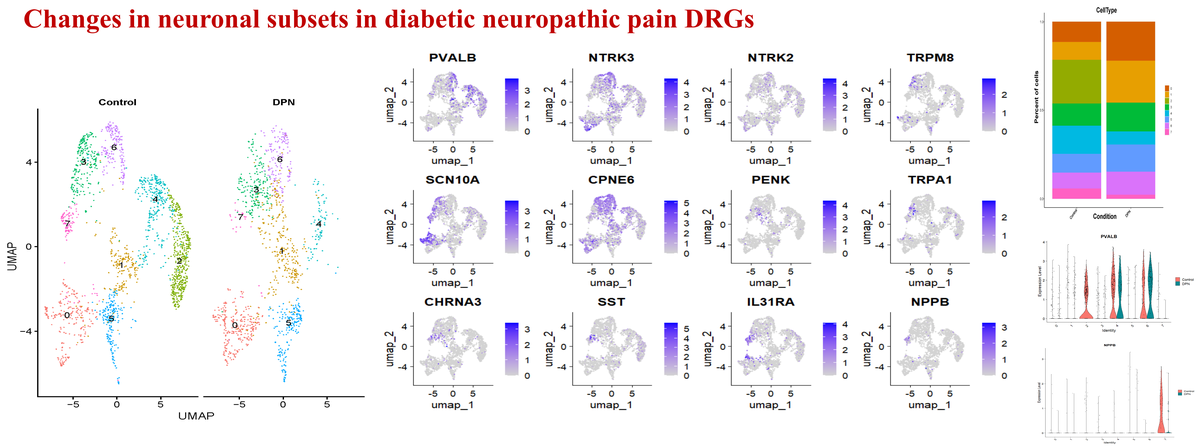
RESULTS

Cell types present in human DRG associated with diabetic peripheral neuropathic pain



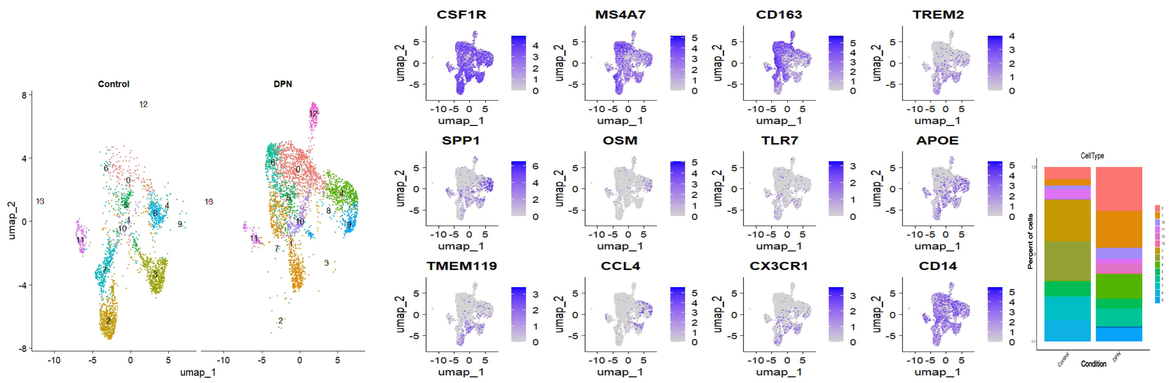
- Seven distinct cell types were identified in DPN DRGs with varied proportions between the two conditions.

Changes in neuronal subsets in diabetic neuropathic pain DRGs



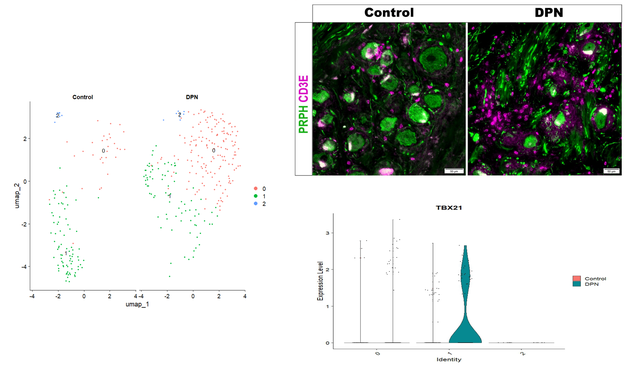
- We identify a reduction in populations in the neuronal subsets clusters (2 and 7) in the DPN DRGs. We observe the loss of PVALB expressing cluster 2 and NPPB expressing cluster 7 in the DPN condition compared to control.

Macrophage phenotypes are significantly changed in DPN samples



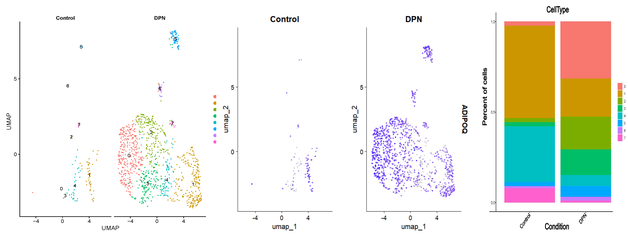
- We observe significant changes in macrophage populations between the conditions.
- Cluster 12, which is increased in DPN shows an enrichment in oxidative stress genes, while clusters 2 and 3 are depleted in DPN and are enriched in genes underpinning the adaptive immune response and TGF-beta signaling.

Increase in Inflammatory T cells in DPN DRGs



- We observe a shift towards inflammatory T cells (TH1) in the DPN DRGs and an increase in the localization of T cells in close proximity to neurons in the DPN DRGs.

Proliferation of Adipocytes in DPN DRGs



- We observe increased numbers of adipocytes expressing high levels of adiponectin but not other adipokines.

CONCLUSION

- Single nucleus sequencing was performed using the 10X FLEX kit on 4 DPN hDRGs and 4 Control hDRGs, with 2 females and 2 males in each condition.
- A notable shift in cell types and significant changes in gene expression were observed between the DPN and Control conditions. Specifically:
  - A loss of certain neuronal populations, most notably proprioceptors, was observed in the DPN DRGs.
  - An increase in inflammatory mediators was noted in both macrophage and T cell populations in DPN DRGs.

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NIH National Institute of Neurological Disorders and Stroke