Report

The potential for retrotransposon mobilisation to modulate sensory loss in ageing.

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1. Introduction

Age affects many processes in the human body and we can see the effects of that ranging from arthritis to dementia. There is every reason to suspect that ageing effects how we feel and respond to pain as we age. These changes should inform how we treat and manage such pain, however rather than just a trial and error approach, a better understanding of the biological changes in the pain pathways associated with ageing will allow a more directed methodology and perhaps novel routes to management.

Our hypothesis is that there are DNA elements in our genome that can sense and respond to pain signals and that they have the potential to not work properly when we age so causing our body to experience pain without the 'normal' external insults or to respond to lower threshold of painful stimuli. We believe these signals in part cause our neurons to function inappropriately and may be considered a normal physiological consequence of ageing.

We are targeting one class of DNA elements known as 'retrotransposons' as being involved in such age related problems. These are elements which are involved in shaping how, where and when our proteins are made in a cell. In the brain their inappropriate regulation associated with ageing has been implicated with neuropsychiatric and neurodegenerative conditions so there is every reason to suspect that a similar mechanism may operate for pain.

To aid our studies and maximise the potential for a legacy that will not only lead to publications and extend our understanding of these elements in pain, we have generated international collaborations with major groups to aid translation of our data to the clinic via both biomarker generation but also potential drugs that could modify these pathways to aid pain relief and other neuronal dysfunction

In summary and outlined below we have ongoing collaborations with

a. Glasgow University – Exploring the expression of retrotransposons in an inflammatory model.
   This model addresses the potential of a novel drug based on a natural product generated by parasites that appears from the literature to delay the ageing process (with related delay of such as arthritis etc.)

b. Pecs University – Exploring the expression of retrotransposons in response to pain stimuli, capsaicin, in dorsal root and trigeminal ganglia. This is the same group I have introduced Dr Goebel to in his fibromyalgia work which is central to PRF strategy.

c. Manchester University – Developing a tagging SNP for use as a potential biomarker of pain phenotype in the ageing population based on retrotransposon polymorphic variation. This would be considered the development of 'normal' pain associated with the ageing process rather than in response to trauma etc.

d. NIH – Exploring functional impact of new genetic variation identified in SVA. This utilises our current work to overlap with Parkinson's disease associated pain. We can access the largest genomic database of Parkinson's patients and controls with sufficient power to address pain within that case group

e. Pharmacogenetics unit UoL, to address the role of retrotransposon genetic variation in efficacy of tramadol treatment in an arthritis study

In all cases manuscripts for publication are being drafted and circulated based on the data that Ms Price has presented in posters or presentations over the last year and highlighted in this document earlier in the 'dissemination' section.

2. The initial target to address our hypothesis, the pain protein termed TRPV1

TRPV1 is a protein that in sensory neurons senses noxious and chemical challenges which allows the periphery to interact with the central nervous system to respond to pain signals. Interestingly it is located in the genome adjacent to a very similar protein, TRPV3, which is involved in the same processes. Noticeably there are differences in how, where and when these two proteins seem to be made in different species, most noticeably in humans and model in which the majority of the work has been done. From our model prospective a major difference is that the human regulatory region contains a human specific retrotransposon, termed an SVA. This SVA could in part account for the differences seen between model and humans as its only present in the human genome. Further as a regulatory domain whose properties could change with age, it is a prime candidate for age associated pain related problems

We have genotyped the key SVA at this locus and are now addressing 1) function of the SVA to direct TRPV1 and 3 gene expression using CRISPR deletion in a clonal cell line and 2) whether the genetic variation is a risk or trend in any of the collaborations addressed in (1) above.

3. The TRPV1/V3 region in our DNA marks a cluster of pain related genes

The DNA region which codes for TRPV1/V3 contains both a clustering of genes involved in pain but also a clustering of SVA elements. There are up to 10 genes/proteins including the TRPVs and 9 SVAs in a relatively small section of our DNA. This suggests the region could be co-ordinately controlled as to when, where and how long these 9 proteins could be made. Further that the SVA elements could

be common mechanism regulating that expression. We are now using computer programmes to access information freely available on the web to determine if that is correct. Our initial analysis is that this may be the case. In such a scenario controlling the function of the SVAs could be a novel avenue in pain control. If this was the case then our genetic tools to address the function of the SVA at the TRPV1/3 region are a route to addressing the efficacy of drugs that could affect SVA function.

4. Models

The SVA elements are human or hominid specific regulatory domains (not in models) and therefore can't directly be analysed in current models of pain. In these models to address the potential for action of retrotransposons in pain we have addressed the expression of the related element termed LINE1. This is a key player in human diseases processes and is a modulator of SVA function. We have addressed LINE1 expression in aging and pain models with collaborators indicated in (1) above.

5. Summary

We have made progress in correlating the SVA element at the TRPV1/3 region as being both a potential biomarker for specific forms of pain and that it is a functional regulator. The SVA is human specific DNA (not found in other species) and therefore offers insight into how humans regulate these genes. For rodent models we can't address the action of such an SVA directly (not present) but as a surrogate addressed function of a related retrotransposon termed LINE1. Our collaborations will allow maximising our work for relevance to pain whilst allowing the legacy of this work to continue once the PhD has finished. The role of retrotransposons in neuronal function is a strong emerging interest with clinical trials initiated to inhibit their function in motor neuron disease. https://mndresearch.blog/2017/09/25/lighthouse-project-shines-a-beacon-on-hervs-and-their-role-in-als/ These drugs will block many different classes of retrotransposon

We hope our work encourages the extension of such studies to consider retrotransposon function in pain as a future target for therapeutic intervention