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 affect how we feel and respond to pain as we age. These changes should inform how we treat and manage such pain, however rather than via trial and error a better understanding of the biological changes in the pain pathways associated with ageing will allow a more directed 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 physiology consequence of ageing.

We are targeting one class of DNA element 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

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

TRPV1 is a protein in sensory neurons that senses noxious and chemical challenges which allows the periphery to interact with the central nervous system to respond to pain signals. Interestingly it is 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 mice in which much 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 these differences between mice 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

2.1. What are we doing?

These SVAs are variable in their DNA sequence and that variation, termed a polymorphism, in SVAs in other genes has been associated with aspects of a disease. Most recently the variation in an SVA that controls a gene involved in X-linked Dystonia Parkinsonism (XDP) has been associated with the age of onset of that condition. This again links more generally the SVA class of element to age related problems. We are therefore defining:

1. The DNA variation of the SVA which sits between the TRPV1 and TRPV3 genes
2. Using genetic tools to address the function of that SVA to change the regulation of TRPV1 and 3.

For the former we are comparing the DNA of people over 55 who have 'age' related pain to those who do not using a collaboration with the University of Manchester who have a study to address age related problems. As part of that study they collect DNA that can be correlated with clinical

records. This study is ongoing but we have demonstrate that the TRPV1/3 SVA is as suspected polymorphic and that variation may allow these elements to work differently in people. Thus we predict that the SVA variation is part of the genetic burden that puts some of us more at risk for age related pain, a so called biomarker for such pain.

In the latter we are using cellular models to address the function of the SVA to change the amount of these proteins in response to pain challenges such as the chill pepper component capsaicin.

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

To our surprise when we looked at the DNA region which coded for TRPV1/V3 we not only observed 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 part 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, 2.1 above, are a route to addressing the efficacy of drugs affect SVA function.

4. The immediate future

To extend and validate our studies on the SVA at this region we have initiated international collaboration that bring added value to the studies in both 1) accelerating the success of our findings and 2) added funding to support our work.

We are working on acquiring the tools and expertise to grow mouse and human neurons in the laboratory by collaboration with Professor Helyes's group in Hungary who have a wealth of experience in pain research. We have for many years had a successful collaboration with this group and indeed we had previously introduced Dr Goebel (Walton) to Professor Helyes to extend his own successful pain research programme. Secondly we have initiated collaboration with Dr Iadarola at the National Institute of Health in USA to access their molecular and biological resources on pain pathways in humans. This will allow us to correlate action of SVAs on the extended TRPV1/3 region encompassing our cluster of pain genes.

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. We have initiated new valuable international collaborations that will have added value to our current studies. We fully expect publications to follow this year however its more important we build critical mass for our projects to maximise its translation not only more widely to the scientific community but its clinical utilisation.