Report
Introduction

We focused on the role of large DNA elements termed 'jumping genes' for their involvement in how we sense and respond to pain pathways. These DNA elements have brought about changes in our genome during evolution to alter where and why genes are produced so generating different levels of proteins in a tissue specific and stimulus inducible manner. This evolutionary process is still very active in humans. Their scientific name is non-LTR retrotransposons and they are established as modulators of changes in the brain and the degeneration of neurons as we age. We postulated that the same mechanism may happen for pain processing and that how these jumping genes function in response to ageing and environment, such as inflammation, may influence how we sense pain. We focused on two main areas to address this hypothesis:

1. A jumping gene of the human specific SVA retrotransposon class, a large 2000+base element that is adjacent in the genome to key pain genes TRPV1 and TRPV3. We predicted it would affect their expression.

2. Another class of retrotransposon termed LINE1 as a sensor of age and inflammation in a rodent model.

Summary of findings and plan for publication.

We have used the tailored genomic technique termed 'CRISPR' to demonstrate the specific removal of a human specific retrotransposon (SVA) as a contributor to regulation of two key pain genes TRPV1 and TRPV3. These are voltage-gated channels and hence the level of these proteins in pain sensing cells in the body will be a key component of how we sense pain (manuscript in preparation).

Polymorphism (changes in genome sequence) in SVAs has been associated with the risk of disease progression and we investigated that in the SVA at the TRPV1/3 location. We demonstrate the SVAs polymorphic nature in the general population and highlight potential genetic variation in this SVA as a risk for altered pain perception. More specifically as capsaicin acts as an agonist of TRPV1 inducing desensitisation and is routinely used for treating neuropathic pain associated with arthritis, we used an arthritis cohort to address SVA polymorphism (manuscript in preparation).

SVA are human specific elements so we could not look at their function in models organisms. To address this we addressed the global gene expression of a retrotransposon class termed LINE1 that is present in both rodents and humans. Studies in rodent models have provided insight into pain mechanisms and demonstrated age associated changes in dorsal root ganglion (DRG) morphology and sensory thresholds that contribute to changes in pain phenotype.

Chronic pain is an age associated disorder and driven in part by the onset of neuroinflammation in the peripheral nervous system. Recent work has identified the expression of LINE1 as an inducer of inflammation in non-pathological ageing. We determined that we could detect and measure LINE1 mRNA expression in DRG. We demonstrated that LINE1 expression correlated with age and linked to an interferon response in a mouse model of inflammatory ageing. We also found that LINE1 expression in mice altered in response to a novel anti-inflammatory drug. The data from this study implies a strong case for further investigation and a potential role in neuroinflammation in the peripheral nervous system (manuscript in preparation).

Our work provides the basis for a wide range of future studies that can further explore the role of retrotransposons in chronic pain that could aid our understanding of species differences, age associated molecular changes and provide an alternative route to develop novel therapeutics. There are several drugs being trialled against LINE1 (which might also affect SVAs) in both cancer and neurodegeneration were the inappropriate expression of LINE1 or SVAs is potentially part of the pathogenic process. A less dramatic but nevertheless inappropriate expression of these jumping genes/retrotransposons could be associated with neuronal dysfunction or inflammatory processes involved in pain.

Dr Price (the PhD student on this project) is taking up a post-doctoral position at National Institute of Health in Washington DC in June 2020 and she will continue to work on SVA function in a variety of models.