The interactive impact of psychological stress and malnutrition on genome stability and telomere integrity

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The telomere is the region of DNA that caps and protects the end of chromosomes. Shorter telomeres, which tend to increase with age, cause increased chromosomal instability (CIN) and DNA damage, and are associated with increased risk of degenerative diseases of ageing. The rate of telomere attrition differs between individuals due to variability in genetic, environmental, dietary and life-style factors. Psychological stress is one factor that has been consistently associated with accelerated telomere shortening. A study conducted by Nobel laureate Prof Elizabeth Blackburn together with Dr Elissa Epel demonstrated that chronically stressed individuals have significantly shorter telomeres than those with lower perceived and/or actual, stress. These findings are consistent with a wealth of evidence suggesting that psychological stress impacts negatively on human health. Certain micronutrients offer protection against CIN and DNA damage. B group vitamins, in particular, are essential both for accurate replication of DNA in dividing cells, and maintenance of methylation (epigenetic) patterns. Disruption of the epigenome through micronutrient deficiency can have serious consequences, leading to potential disease initiation. Accordingly, the central aim of this project was to determine how stress hormones impact on human health, at the molecular level, and to determine whether practical, nutritional measures could protect against stress-induced chromosomal damage.

In the course of this fellowship several new capabilities were developed, and implemented, including measurement of DNA methylation status, long term tissue culture for nutriome and stress studies using primary human immune cells (lymphocytes), and a fluorescence *in situ* hybridisation (FISH) method which was established and successfully applied allowing detection of centromeric and telomeric DNA with fluorescence microscopy. Data generated with these methods has been central to success of the SIEF PDF project, and has featured in several of the publications arising from this work.

The central hypothesis, that stress hormones directly induce chromosomal, telomeric and epigenetic instability, was tested using both *in vivo* and *in vitro* methods. Novel findings from the latter indicated that the stress hormone, cortisol, is unlikely to be the mediating factor for telomere shortening observed in stressed individuals. The PDF was awarded a travel grant to present these findings at an international scientific meeting, and a manuscript is currently at final draft stage prior to submission to a high impact, peer reviewed journal.

The second (major) component of the fellowship involved the design and implementation of a human study to examine the impact of stress and nutritional status in a cohort of 42 individuals, each of whom is the primary carer for a family member with dementia. Their results were compared with those of non-carers matched for age, gender and body mass index (BMI). The study design was highly innovative, examining stress hormones in different tissues (hair, saliva and plasma), self-reported psychological, lifestyle and dietary intake data, together with a comprehensive panel of molecular and physiological measures; telomere length, DNA damage, epigenome status, plasma micronutrient status, immune cell ratios, and inflammatory cytokines. Important novel findings arising from this work include a highly significant, positive association between psychological stress and DNA damage, and a negative relationship between stress hormones and telomere length. Micronutrient status and several nutritional factors were lower in carers than controls, while potentially harmful metabolites were elevated, and significantly associated with stress measures.