The role of calpain and calpastatin in cancer biology and cellular ageing.

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The calpains are becoming increasingly recognised for the important role they play in numerous diseases, including cancer. They are a family of neutral cysteine proteinases that cleave various substrates involved in cytoskeletal remodelling, migration, cell signalling and apoptosis/survival. There are at least 14 calpain isoform genes, however the most commonly described enzymes are the ubiquitously expressed micro (μ)- and milli (m)-calpain (calpain-1 and -2). In cancer, expression and activity of the calpains are altered and this has been shown to influence cell migration using in-vitro models. The calpain-specific endogenous inhibitor calpastatin is the main regulator of calpain activity. In a majority of tissues calpastatin is in excess of calpain therefore it must become separated (spatially/ temporally) to permit enzyme activity. An imbalance between calpain and calpastatin is believed to be a factor in a number of disease pathologies. Calpastatin is a relatively understudied molecule in cancer – the current proposal will address this. There is one human gene encoding calpastatin, however there are three isoforms (Types) resulting from differential promoter usage, and numerous splice variants. Preliminary data suggest that experimental manipulation of calpastatin can affect cell function.

The heterogeneity and differential expression of CAST mRNA and protein variants appears to have functional significance as exemplified by recent gene expression analysis we conducted in early stage breast cancer patients. It is unclear what function of calpastatin may be influenced through the presence or absence of particular exons, however Ex6 has been shown to modulate intracellular movement and Ex3 is postulated to modulate intracellular location. In addition to influencing lymphovascular invasion (LVI, one of the earliest steps in metastasis), we have also recently shown that calpain system expression plays an important role in predicting the response to certain anticancer therapies. Such results point to the importance of the system in cancer, both in terms of disease progression, metastasis and also response to therapies. As indicated above, little is known about calpastatin expression and localisation in relation to calpain expression, localisation and function with nothing previously being conducted in breast or ovarian cancer – the current proposal will address this. As CAST expression is important for regulating calpain activity we believe that manipulation of this system poses an important therapeutic target.

We aim to understand the heterogeneity of human calpastatin expression in breast, ovarian and brain cancers and establish the mechanisms by which this alters calpain activity. The importance of calpain and calpastatin expression in regulating progression and therapy response (radiotherapy, chemotherapy) will be examined via IHC and in vitro approaches. The role that the calpain/calpastatin axis plays in regulating cell aging will also be studied using a variety of 'normal' cell systems.

Please **email a CV with a covering letter** to Dr Stewart Martin (stewart.martin@nottingham.ac.uk), who can also supply more information to interested parties.