Cathepsin G – A Novel Protease in the Regulation of Chronic Pain

Xiaodong Liu, Ph.D.[1], Yuanyuan Tian, Ph.D.[1], Yan Chen, M.Sc.[1], Tony Gin, M.D.[1], Christopher HK Cheng, Ph.D.[2], Matthew TV Chan, FANZCA[1]

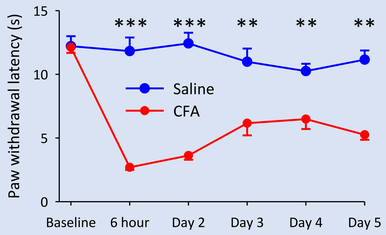
[1]Anaesthesia and Intensive Care, Chinese University of Hong Kong, Shatin, NT Hong Kong, [2]School of Biomedical Sciences, Chinese University of Hong Kong, Shatin, NT, Hong Kong SAR

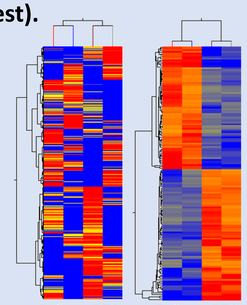
Background and Aims

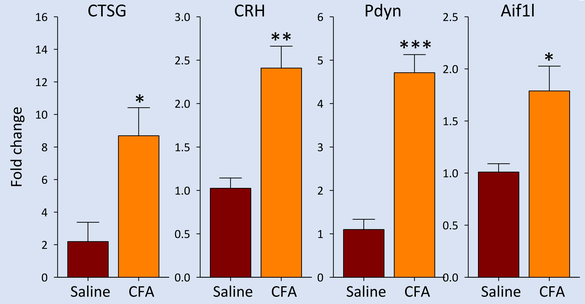
Proteases have been shown to modulate pain signaling in central sensitization. We aimed to identify the protease network during the development of chronic pain using a genome-wide screening approach. In this study, we determined the role of cathepsin G (CTSG) as a novel protease in the modulation of spinal pain signaling in animal pain model and postsurgical patients.

Methods and Results

We conducted a microarray analysis of spinal dorsal horn in rats with chronic inflammatory pain after intraplantar injection of complete Freund's Adjuvant (CFA). We found that the expression of *CTSG* was the most up-regulated candidate gene (4.7 fold, $p = 0.0003$) in CFA rats ($n = 4$) compared with control ($p = 0.0001$, repeated measures ANOVA, $^{**}p < 0.01$, $^{***}p < 0.001$, compared with saline controls, unpaired t test).

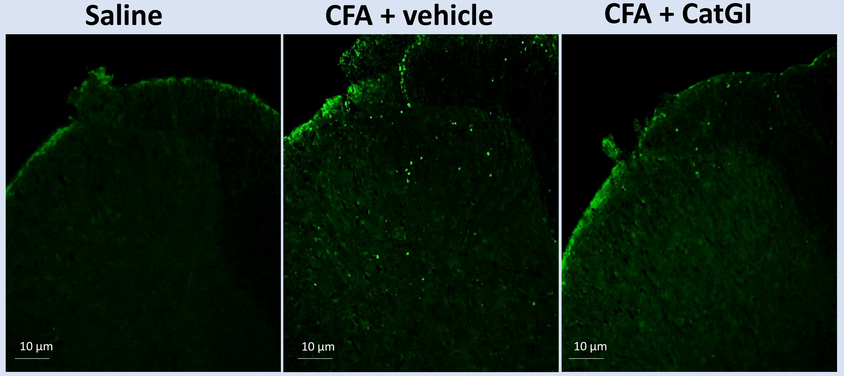


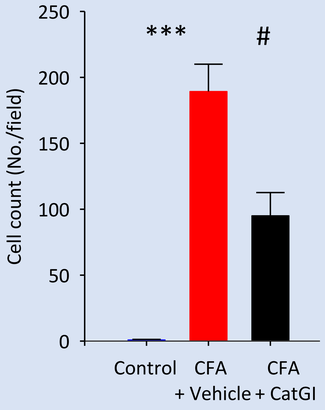


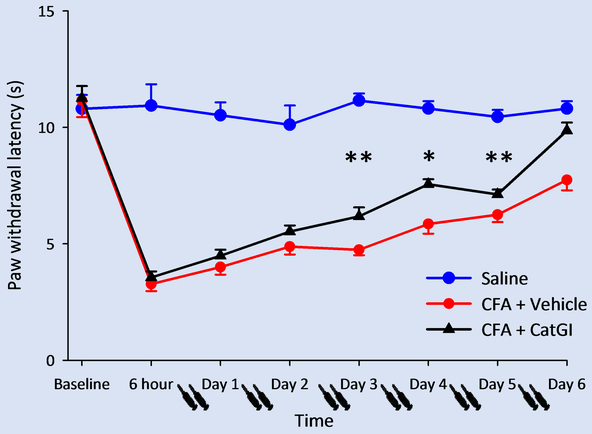


Using an intrathecal catheter, we injected twice daily a specific CTSG inhibitor (CatGI) or saline vehicle to rats with CFA induced chronic inflammatory pain. Heat hyperalgesia was determined by using plantar analgesia meter.

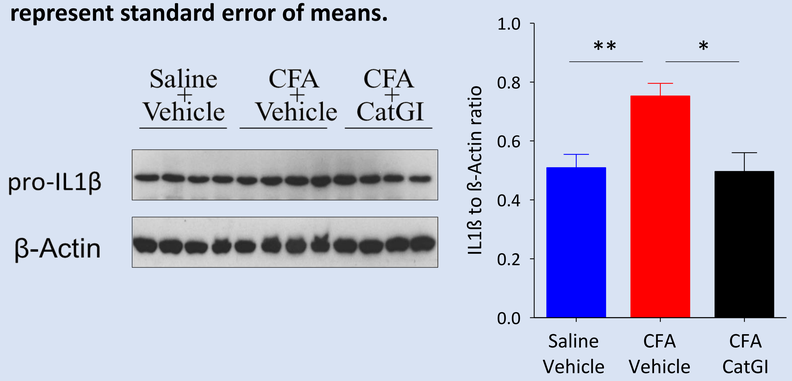
Inhibition of CTSG reduced heat hyperalgesia. $n = 10$ in each group, $p < 0.001$, repeated measures ANOVA. $^{*}p < 0.05$, $^{**}p < 0.01$, unpaired t test. This was contributed by the reduction in neutrophil infiltration (stained with myeloperoxidase – green)







There was also a decrease of IL 1β protein levels in the spinal dorsal horn, $^{**}p < 0.01$ compared with saline with vehicle group, and $^{*}p < 0.05$ compared with CFA with vehicle group, unpaired t test. Error bars represent standard error of means.



We also genotyped all known variants in the *CTSG* gene (with minor allele frequency ≥ 5% in Chinese Hans) in 1,152 consecutive surgical patients. 246 patients (21.4%) reported persistent pain at 12 months after surgery (using modified brief pain inventory). Polymorphisms of two *CTSG* genes were associated with a lower risk of chronic postsurgical pain [*rs2070697*, odds ratios (95%CI): 0.64 (0.43-0.96); *rs2236742*, odds ratio (95%CI): 0.27 (0.16-0.46)].

Conclusions

Our study demonstrated that CTSG is a pro-nociceptive mediator in animal CFA-induced pain model and patients undergoing a variety of surgery. CTSG represents a new target for pain control and a potential marker to predict patients who are prone to develop chronic pain.

Acknowledgments

This work was supported by a General Research Fund (461510), Research Grant Council, Hong Kong SAR and an Academic Enhancement Grant of the Australian and New Zealand College of Anaesthetists (AEG13/001).