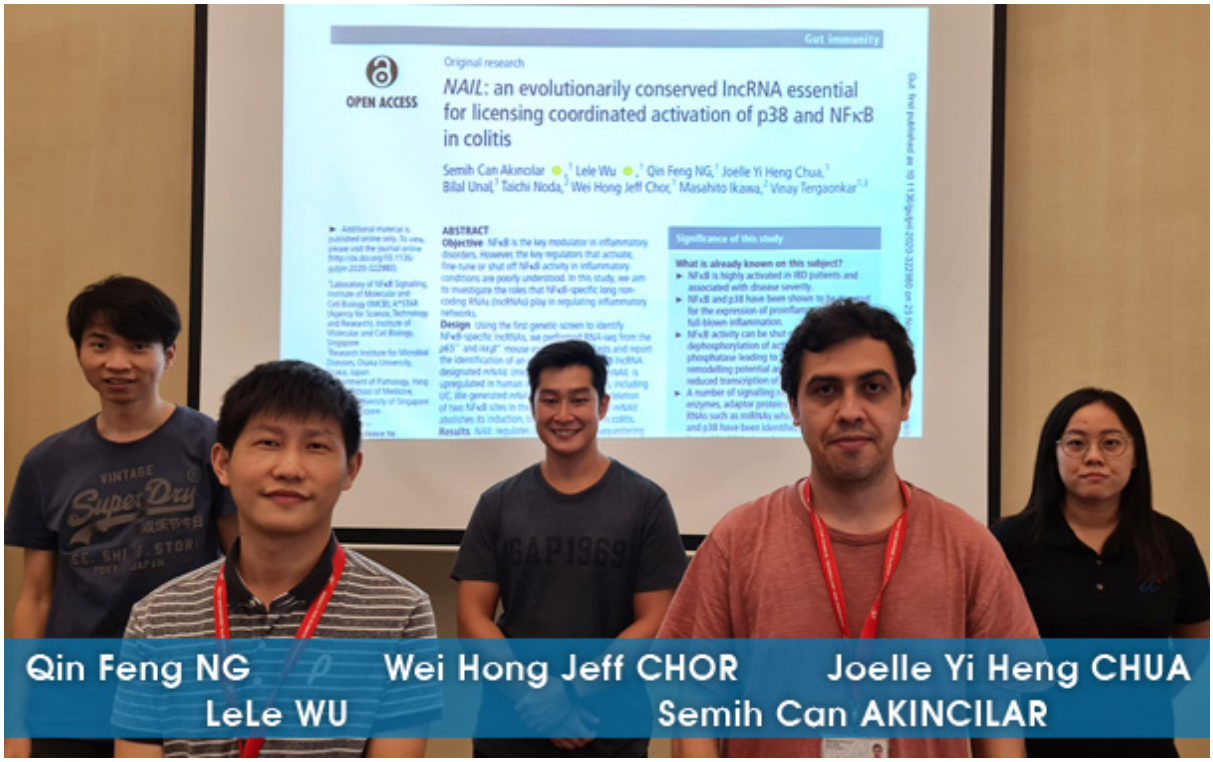
# *NAIL*: an evolutionarily conserved lncRNA essential for licensing coordinated activation of p38 and NFκB in colitis

**Tuesday, 01 Dec 2020**




**Authors**

Semih Can Akıncılar [1], Lele Wu [1], Qin Feng NG [1], Joelle Yi Heng Chua [1], Bilal Unal [1] , Taichi Noda [2], Wei Hong Jeff Chor [1], Masahito Ikawa [2] and Vinay Tergaonkar [1,3]

[1] Laboratory of NFκB Signalling, Institute of Molecular and Cell Biology (IMCB), A*STAR (Agency for Science, Technology and Research), Institute of Molecular and Cell Biology, Singapore

[2] Research Institute for Microbial Diseases, Osaka University, Osaka, Japan

[3] Department of Pathology, Yong Loo Lin School of Medicine, National University of Singapore (NUS), Singapore

Correspondence to Vinay Tergaonkar,
Institute of Molecular and Cell Biology, 138673, Singapore; vinayt@imcb.a-star.edu.sg

**Published online in *GUT* on 25 November 2020**

**https://doi.org/10.1136/gutjnl-2020-322980**

**Abstract**

NFκB is the key modulator in inflammatory disorders. However, the key regulators that activate, fine-tune, or shut off NFκB activity in inflammatory conditions are poorly understood. Using the first genetic-screen to identify NFκB-specific lncRNAs, we performed RNA-seq from the *p65*$^{-/-}$ and *Ikkβ*$^{-/-}$ MEFs and report the identification of an evolutionary conserved lncRNA designated *mNAIL* (mice), or *hNAIL* (human). *hNAIL* is upregulated in human inflammatory disorders, including ulcerative colitis. We generated *mNAIL*$^{\Delta NF\kappa B}$ mice, wherein deletion of 2 NFκB sites in the proximal promoter of *mNAIL* abolishes its induction, to study its function in colitis.

*NAIL* regulates inflammation via sequestering and inactivating Wip1, a known negative regulator of pro-inflammatory p38 kinase and NFκB subunit p65. Wip1 inactivation leads to co-ordinated activation of p38 and co-valent modifications of NFκB, essential for its genome-wide occupancy on specific targets. *NAIL* enables an orchestrated response for p38 and NFκB co-activation that leads to differentiation of precursor cells into immature myeloid cells in bone marrow, recruitment of macrophages to inflamed area and expression of inflammatory genes in colitis.

*NAIL* directly regulates initiation and progression of colitis and its expression is highly correlated with NFκB activity which makes it a perfect candidate to serve as a biomarker and a therapeutic target for IBD and other inflammation associated diseases.

**Figure**

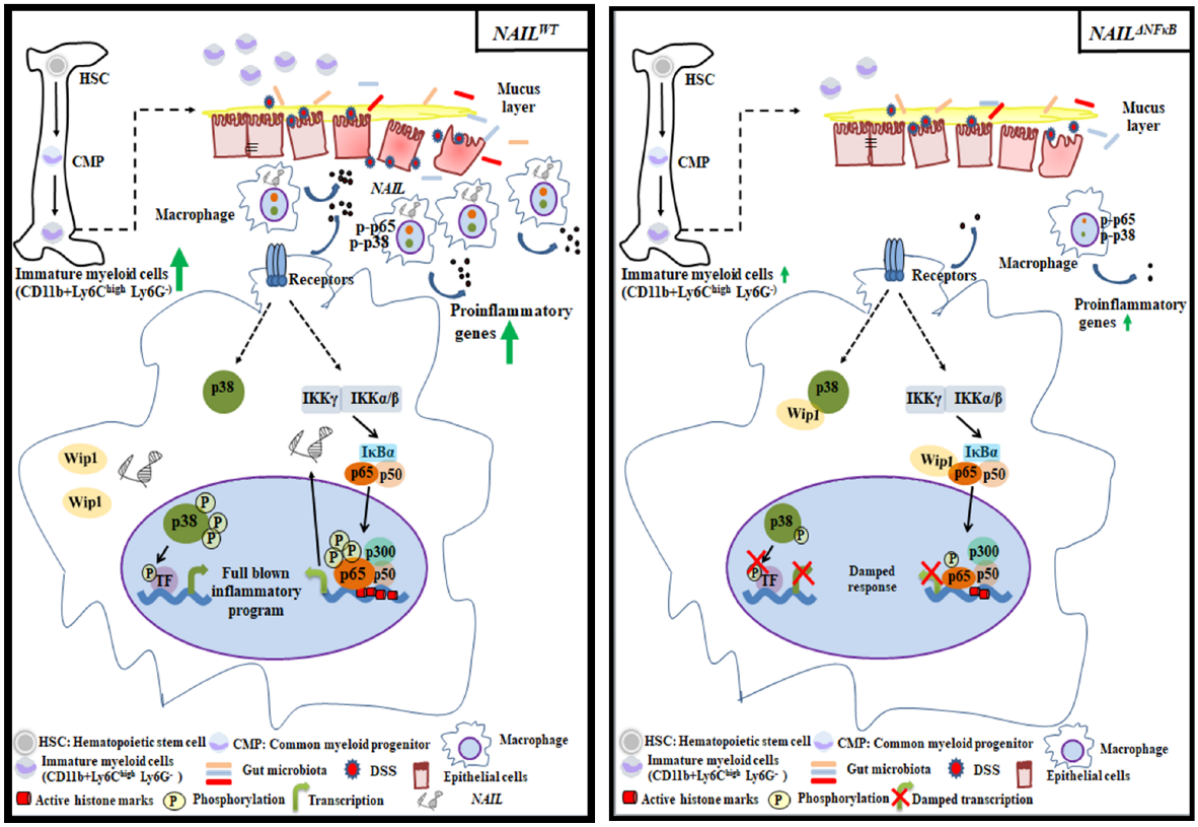



**Figure 7: *mNAIL* sequesters Wip1 phosphatase away from its substrate *in vivo.***

In the colitis model, in the presence of *NAIL*, activation of p38 and p65 is co-ordinated in a timely manner. Upon intestinal damage and release of microbiota to the colon, myeloid progenitor cells differentiate into immature myeloid cells which give rise to macrophages that infiltrate inflamed colon and express inflammatory genes. In the absence of *NAIL*, Wip1 prevents phosphorylation of p65 and p38 which leads to defects in generation of immature myeloid cells, reduction of recruitment of macrophages and deregulated expression of inflammatory genes.