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Topic Category: 4131-ASIP Signal transduction in cancer

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Presentation Preference: Oral

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Sponsor's Society: Biochemistry - American Society for Biochemistry and Molecular Biology (ASBMB) - Host Society
Keywords: 1. NFkb 2. PrP 3. CYLD

Prion protein is required for tumor necrosis factor alpha (TNFα)-triggered nuclear factor kappa B (NF-κB) signaling and cytokine production.

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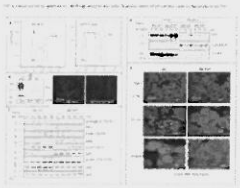
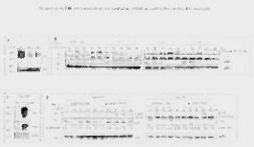
Cellular prion protein (PrP^C) is a widely expressed, highly conserved glycosylphosphatidylinositol (GPI) anchored protein among mammlian. In some cancer cells, PrP exists as pro-PrP, retaining its GPI-peptide signaling sequence and localizing outside of lipid rafts.

In M2 cells, TNFα upregulates the expression of phosphorylated (p)-IκB-kinase α/β (p-IKKα/β), p-p65, and p-JNK, but downregulates the IκBα protein, all of which are downstream signaling intermediates in the TNF receptor signaling cascade. When *PRNP* is deleted in M2 cells, the effects of TNFα are no longer detectable. More importantly, p-p65 and p-JNK responses are restored when *PRNP* is re-introduced back into the *PRNP* null cells. TNFα also activates NF-κB and increases TNFα production in wildtype M2 cells, but not in PrP-null M2 cells. Similar results are obtained in the BxPC-3 cells. Moreover, TNFα activation of NF-κB requires ubiquitination of receptor-interacting serine/threonine kinase 1 (RIP1) and TNF receptor–associated factor 2 (TRAF2). TNFα treatment increases the binding between PrP and the deubiquitinase tumor suppressor cylindromatosis (CYLD). In these treated cells, binding of CYLD to RIP1 and TRAF2 is reduced. We conclude that PrP traps CYLD, preventing it from binding and deubiquitinating RIP1 and TRAF2, thus activating NF-κB signaling.

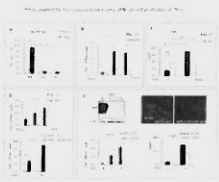
These results reveal that PrP enhances the responses to TNFα, promoting proinflammatory cytokine production, which may contribute to inflammation and tumorigenesis.



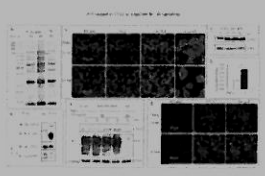
PrP is required for responses to TNFR signaling in M2 cells



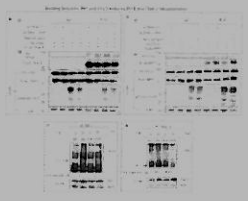
Response to TNFα treatment is rescued when PRNP is reintroduced into PrP null cells



PrP is required for the downstream activity of NF-κb and production of TNFα



PrP bound to CYLD to regulate NF-κb signaling



Binding between PrP and CYLD reduces RIP1 and TRAF2 ubiquitination

A model to describe how PrP affect NFkb signaling

Support or Funding Information
1.NSFC (Awarded number: 81172376)： pro-prion contributes to PDAC tumorigenesis. 2.NSFC（Awarded number：31670170）： Def of GPI Anchor Synthesis Leading to Generation of Pro-PrP.

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