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Previous work in our laboratory has shown that tumour-necrosis factor receptor 1 (TNFR1) is a novel substrate for Presenilin 1 (PS1)-containing γ-secretase protease complexes. In this study, we investigated the functional consequence of γ-secretase-mediated cleavage of TNFR1 on the assembly of the TNFR1-signaling complexes and promotion of apoptotic and inflammatory signalling using presenilin-deficient fibroblasts, we demonstrate reduced formation of TNFR1-associated death-inducing signalling complex II and increased resistance to tumour necrosis factor alpha (TNFα)/cycloheximide-induced apoptosis, thus the presenilins and γ-secretase act as intracellular regulators of TNFR1-mediated pro-apoptotic signalling pathways.

Secondly, given the previously published work by our laboratory demonstrating a γ-secretase independent role of Presenilin 2 (PS2) in tumour necrosis factor-α (TNF-α), interleukin-1 Beta (IL-1β)-and lipopolysaccharide (LPS)-mediated signalling (Agrawal et al., 2015), we investigated whether gene silencing of PS2 antagonised toll-like receptor 4 (TLR4)-mediated inflammatory responses in human macrophages. We show that in response to stimulation with LPS, human macrophages with reduced PS2 expression have impaired responsiveness to LPS by differential activation of nuclear factor-κβ (NF-κB) and mitogen-activated protein kinases (MAPK). However, LPS-induced cytokine production of pro- and anti-inflammatory cytokines was not altered.

Finally, γ-secretase activity is also known to be an important event for pathogen receptors (Coleman-Vaughan et al., 2017). To determine the conservation of regulated intramembrane proteolysis (RIP) as a physiological occurrence amongst viral receptors, we demonstrate for the first time that Angiotensin-converting enzyme 2 (ACE2), the severe acute respiratory syndrome (SARS) coronavirus receptor, is a substrate for γ-secretase dependent proteolysis.