PYPAF3, a PYRIN-containing Apaf-1-like protein, is a feedback regulator of caspase-1-dependent interleukin-1β secretion

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PYPAF3 is a member of the PYRIN-containing apoptotic protease-activating factor-1-like proteins (PYPAFs) that are thought to function in inflammatory signaling pathways. Among the members of this family, PYPAF1, PYPAF5, PYPAF7, and NALP1 have been shown to induce caspase-1-dependent interleukin-1β secretion and NF-κB activation in the presence of the adaptor molecule ASC. On the other hand, we recently identified PYNOD, another member of this family, as a suppressor of these responses. In this study, we showed that PYPAF3 is the second member that inhibits caspase-1-dependent interleukin-1β secretion (Fig. 1) and that PYPAF2 does not inhibit this response, but rather inhibits the ASC-mediated NF-κB activation (Fig. 2). Both PYPAF2 and PYPAF3 mRNAs are broadly expressed in a variety of tissues; however, neither is expressed in skeletal muscle, and only PYPAF2 mRNA is expressed in heart and brain. They are also expressed in many cell lines of both haematopoietic and non-haematopoietic lineages. Stimulation of monocytic THP-1 cells with lipopolysaccharide or interleukin-1β induced PYPAF3 mRNA expression (Fig. 3). Furthermore, the stable expression of PYPAF3 in THP-1 cells abrogated the cells' ability to produce interleukin-1β in response to lipopolysaccharide. These results suggest that PYPAF3 is a feedback regulator of interleukin-1β secretion. Thus, PYPAF2 and PYPAF3, together with PYNOD, may constitute an anti-inflammatory subgroup of PYPAFs. (Kinoshita, T. et al., J. Biol. Chem. 280:21720-5, 2005)

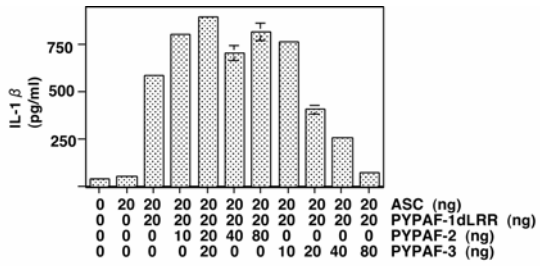

Fig. 1. PYPAF3 inhibits caspase-1-dependent IL-1 β secretion.

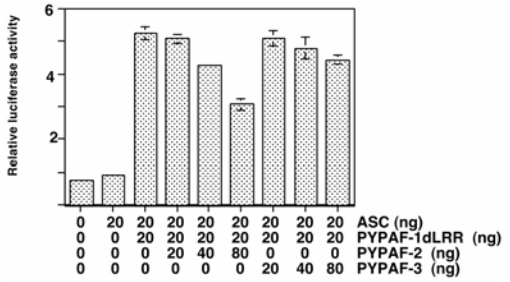

Fig. 2. PYPAF2 inhibits ASC-mediated NF- κ B activation.

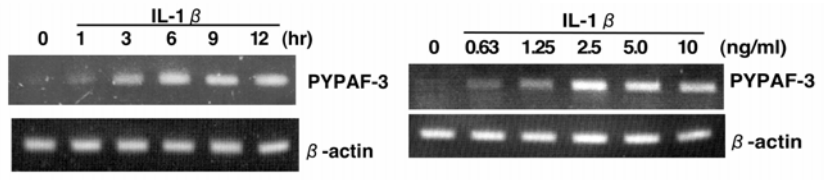

Fig. 3. IL-1 β induces expression of PYPAF3 mRNA in THP-1 cells.