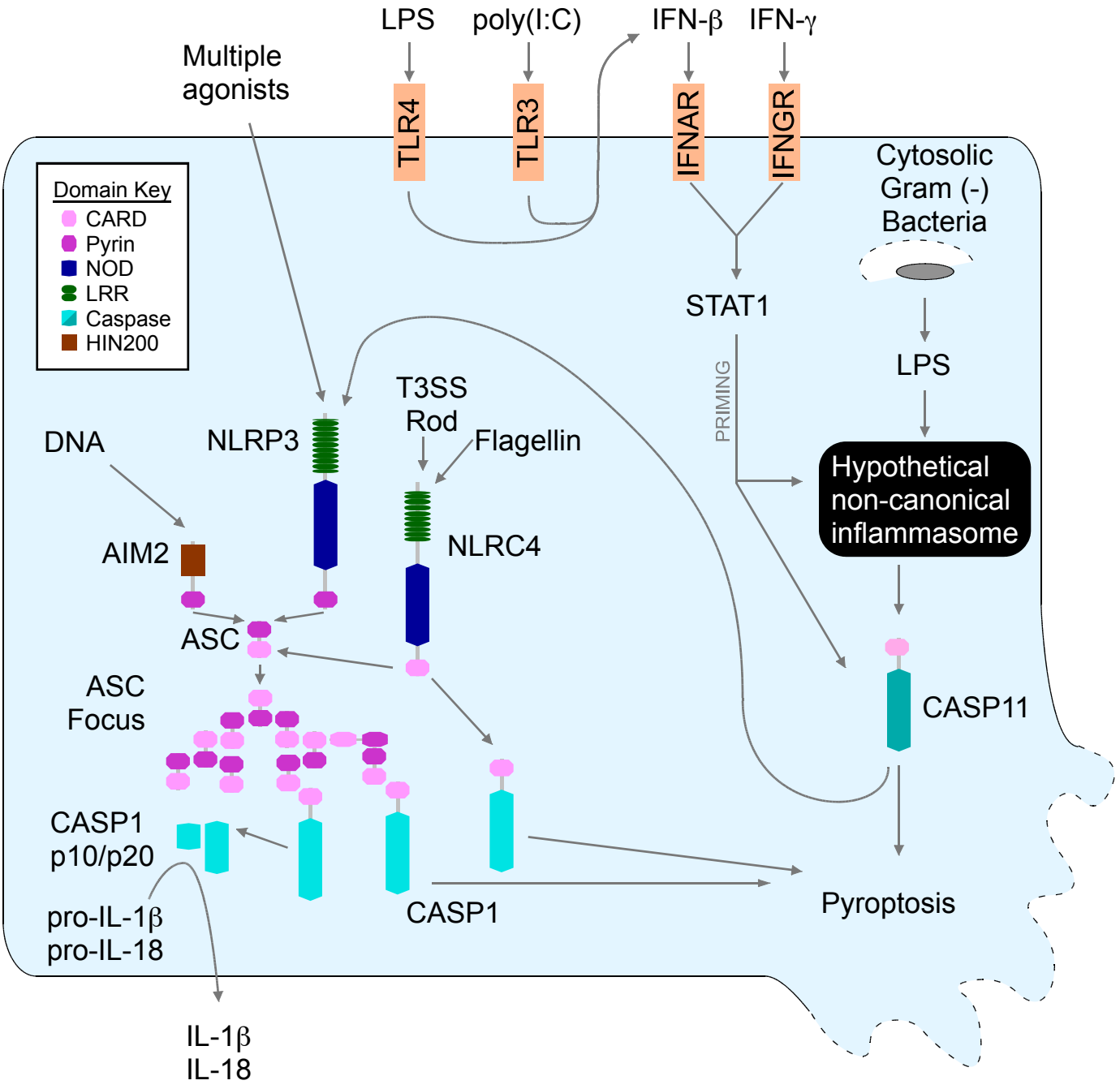

Figure S1.Schematic of canonical and non-canonical inflammasome pathways. The canonical inflammasomes (shown here: NLRP3, AIM2, and NLRC4) activate caspase-1, whereas a hypothetical non-canonical inflammasome activates caspase-11. Both caspase-1 and caspase-11 initiate pyroptosis. Via its CARD domain, NLRC4 can directly bind caspase-1 to mediate its activation. In contrast, Pyrin domain containing inflammasomes, such as NLRP3 and AIM2, cannot directly bind caspase-1; rather, they interact indirectly via the adaptor protein ASC, which polymerizes into a structure called the ASC focus. Caspase-1 processes IL-1β and IL-18 to their mature secreted forms in the ASC focus. In contrast, caspase-11 does not process IL-1β alone, rather it activates the NLRP3/ASC/caspase-1 pathway (arching arrow). In the absence of *Nlrc4* and *Asc*, macrophages are unable to signal via almost all known canonical inflammasome pathways; however, they retain the ability to activate caspase-11, which functions independently of the canonical inflammasomes. *Casp1*$^{-/-}$*Casp11*$^{-/-}$ macrophages, on the other hand, are deficient in all inflammasome pathways.

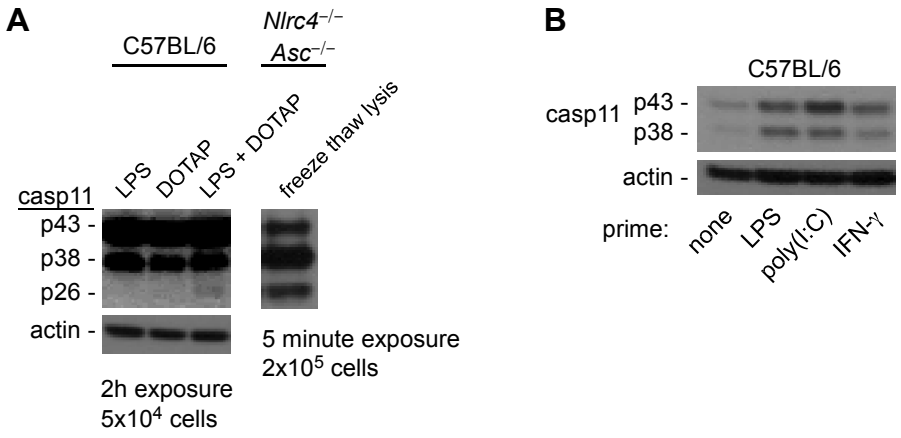

Fig. S2. Upregulation of caspase-11 potentiates pyroptosis but not proteolytic processing. (**A**, left) Overexposure of caspase-11 western blot from Fig. 1F reveals minor processing of caspase-11 in LPS primed C57BL/6 BMMs 2 hours after transfection with LPS. (**A**, right) *Nlrc4*$^{-/-}$*Asc*$^{-/-}$ BMMs (2 x 10^5 cells in 5μL endotoxin free water + protease inhibitor) were subjected to three freeze thaw cycles. Insoluble components were pelleted and supernatants were then incubated for 5 minutes at 37°C. SDS-sample buffer was added to the reaction and then processed for western blotting. Significant spontaneous processing was observed in the lysates. Interpretation of (**A**, left): Although the minor processed band observed after LPS transfection could represent caspase-11 processing in response to cytosolic LPS, it could also be due to spontaneous processing that occurs in the media after pyroptotic cell lysis. (**B**) Upregulation of full-length caspase-11 in unprimed BMMs, or BMMs primed overnight with LPS (50ng/mL), poly(I:C) (1000ng/mL), or IFN-γ (8ng/mL), as revealed by western blot.