Inflammasome activators induce interleukin-1β secretion via distinct pathways with differential requirement for the protease function of caspase-1.

Through their capacity to sense danger signals and to generate active interleukin-1β (IL-1β), inflammasomes occupy a central role in the inflammatory response. In contrast to IL-1α, little is known about how IL-1β is regulated. We found that all inflammasome activators also induced the secretion of IL-1β, leading to the cosecretion of both IL-1 cytokines. Depending on the type of inflammasome activator, release of IL-1β was inflammasome dependent or independent. Calcium influx induced by the opening of cation channels was sufficient for the inflammasome-independent IL-1β secretion. In both cases, IL-1β was released primarily in a processed form, resulting from intracellular cleavage by calpain-like proteases. Inflammasome-caspase-1-dependent release of IL-1β and IL-1β was independent of caspase-1 catalytic activity, defining a mode of action for caspase-1. Because inflammasomes contribute to the pathology of numerous chronic inflammatory diseases such as gout and diabetes, IL-1β antagonists may be beneficial in the treatment of these disorders.