β2-microglobulin - a trigger for NLRP3 inflammasome activation in tumor-associated macrophages promoting multiple myeloma cell progression

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Pro-inflammatory macrophages, as significant constituents of the tumor microenvironment in multiple Myeloma (MM), are key promoters of disease progression, bone destruction, and immune-impairment. Consequently, the identification of endogenous mediators of these inflammatory processes open novel therapeutic avenues against major pathological features of MM. We identify beta-2-microglobulin (β2m) as an important driver in the initiation of inflammation in myeloma-associated macrophages (MAMs). Lysosomal accumulation of phagocytosed β2m in patient derived MAMs promoted β2m amyloid aggregation, resulting in lysosomal rupture and ultimately in the production of active interleukin (IL)-1b and IL-18. Interestingly, this process strictly depended on the activation of the NALP3 inflammasome after β2m accumulation. Moreover, depletion or silencing of β2m in MM cells abrogated inflammasome activation in a murine MM model. Finally, the specific disruption of NLRP3 or IL-18 diminished tumor growth and osteolytic bone destruction normally promoted by β2m-induced inflammasome signaling. Taken together our results provide novel mechanistic evidence for β2m's role as an NALP3 inflammasome activator during MM pathogenesis. Moreover, inhibition of NALP3 highlights one potential novel therapeutic approach to combat this severe malignancy.

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