The impact of proteasome impairment on microglia function and neuroinflammation

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Cellular protein homeostasis is maintained by the ubiquitin proteasome system (UPS) via protein ubiquitylation and proteasomal degradation. In response to inflammation, catalytic β-subunits of the standard proteasome (SP) are replaced by the inducible subunits and form an alternative isoform, the immunoproteasome (IP). Proteasome (IP and SP) dysfunction results in accumulation of ubiquitylated proteins, the induction of type I interferons (IFNs), and systemic inflammation including neuroinflammation (Previously published in: Brehm A et al. (2015) J Clin Invest 125, 4196-211). Microglia are immune cells of myeloid origin in the brain which constitutively express IP. Since our understanding of the impact of proteasome impairment on microglia function is very limited, we sought to determine the molecular link between ubiquitin-conjugate accumulation following proteasome dysfunction and neuroinflammation. In order to mimic inflammation, we subjected primary microglia isolated from wild type and LMP7 knockout mice, which harbor a deletion of the *PSMB8* gene encoding the IP catalytic subunit LMP7, to treatment with the proteasome inhibitor bortezomib (BTZ) and the toll-like receptor 4 ligand lipopolysaccharide (LPS). BTZ treatment induced type I IFNs dependent on the IRE1-arm of the unfolded protein response in wild type microglia (Previously published in: Studencka-Turski M, Çetin G et al. (2019) Frontiers Immunol doi: 10.3389/fimmu.2019.02900). LPS treatment caused an accumulation of ubiquitylated proteins in primary microglia of both genotypes, however cells with impaired IP function exhibited more of the ubiquitin-conjugates. Moreover, molecular analysis revealed significantly stronger induction of inflammation, as indicated by higher levels of type I IFNs and interferon-stimulated genes in primary microglia with IP impairment. In an attempt to identify the drivers of the inflammation, the ubiquitylated proteins will be characterized further by proteomic analysis.