Aggresome

In eukaryotic cells, an aggresome refers to an aggregation of misfolded proteins in the cell, formed when the protein-degradation system of the cell is overwhelmed. Aggresome formation is a highly regulated process that possibly serves to organize misfolded proteins into a single location.

Despite the role of misfolded/aggregated proteins in neurological disorders, their role in cancer pathogenesis is poorly defined.

Results support the role of aggresome as a novel prognostic molecular marker for pediatric choroid plexus tumors (CPTs) that was comparable to the molecular classification in segregating samples into two distinct subgroups, and to the pathological stratification in the prediction of patients' outcomes. Moreover, the proteogenomic signature of CPTs displayed altered protein homeostasis, manifested by enrichment in processes related to protein quality control [1)].

In the current study we aimed to investigate whether aggresomes-positivity could be used to improve the disease subclassification and prognosis prediction of pediatric medulloblastoma. Ninety three pediatric medulloblastoma tumor samples were retrospectively stratified into three molecular subgroups; WNT, SHH and non-WNT/non-SHH, using immunohistochemistry and Multiplex Ligation Probe Amplification. Formation of aggresomes were detected using immunohistochemistry. Overall survival (OS) and event-free survival (EFS) were determined according to risk stratification criteria. Multivariate Cox regression analyses were carried out to exclude confounders. Aggresomes formation was detected in 63.4% (n = 59/93) of samples. Aggresomes were non-randomly distributed among different molecular subgroups (P = 0.00002). Multivariate Cox model identified aggresomes' percentage at ≥20% to be significantly correlated with patient outcome in both OS (HR = 3.419; 95% CI, 1.30-8.93; P = 0.01) and EFS (HR = 3; 95% CI, 1.19-7.53; P = 0.02). The presence of aggresomes in ≥20% of the tumor identified poor responders in standard risk patients; OS (P = 0.02) and EFS (P = 0.06), and significantly correlated with poor outcome in non-WNT/non-SHH molecular subgroup; OS (P = 0.0002) and EFS (P = 0.0004) [2)].

1: Kundu A, Milosch N, Antonietti P, Baumkötter F, Zymny A, Müller UC, Kins S, Hajieva P, Behl C, Kögel D. Modulation of BAG3 Expression and Proteasomal Activity by sAPPα Does Not Require Membrane-Tethered Holo-APP. Mol Neurobiol. 2016 Nov;53(9):5985-5994. doi: 10.1007/s12035-015-9501-y. Epub 2015 Nov 2. PubMed PMID: 26526841.

2: Baets J, Duan X, Wu Y, Smith G, Seeley WW, Mademan I, McGrath NM, Beadell NC, Khoury J, Botuyan MV, Mer G, Worrell GA, Hojo K, DeLeon J, Laura M, Liu YT, Senderek J, Weis J, Van den Bergh P, Merrill SL, Reilly MM, Houlden H, Grossman M, Scherer SS, De Jonghe P, Dyck PJ, Klein CJ. Defects of mutant DNMT1 are linked to a spectrum of neurological disorders. Brain. 2015 Apr;138(Pt 4):845-61. doi: 10.1093/brain/awv010. Epub 2015 Feb 11. PubMed PMID: 25678562; PubMed Central PMCID: PMC5014076.

Renziehausen J, Hiebel C, Nagel H, Kundu A, Kins S, Kögel D, Behl C, Hajieva P. The cleavage product of amyloid-β protein precursor sAβPPα modulates BAG3-dependent aggresome formation and enhances cellular proteasomal activity. J Alzheimers Dis. 2015;44(3):879-96. doi: 10.3233/JAD-140600. PubMed PMID: 25362034.

1)
Amer N, Taha H, Hesham D, Al-Shehaby N, Mosaab A, Soudy M, Osama A, Mahmoud N, Elayadi M, Youssef A, Elbeltagy M, Zaghloul MS, Magdeldin S, Sayed AA, El-Naggar S. Aggresomes predict poor outcomes and implicate proteostasis in the pathogenesis of pediatric choroid plexus tumors. J Neurooncol. 2021 Jan 26. doi: 10.1007/s11060-020-03694-3. Epub ahead of print. PMID: 33501605.
2)
Yehia M, Taha H, Salama A, Amer N, Mosaab A, Hassanain O, Refaat A, Yassin D, El-Hemaly A, Ahmed S, El-Beltagy M, Shaalan O, El-Naggar S. Association of Aggresomes with Survival Outcomes in Pediatric Medulloblastoma. Sci Rep. 2019 Aug 30;9(1):12605. doi: 10.1038/s41598-019-49027-x. PubMed PMID: 31471537.