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Topic of Research: Design and Development of Tau-Protein Kinase Inhibitors for Therapeutic Targeting of Neuroinflammatory Diseases

Keywords: Tauopathy; Neuroinflammation; Tau hyperphosphorylation; Alzheimer's Disease; DYRK1A; ABL1; TTBK1; Natural Products; Virtual Screening; Molecular Dynamics Simulation; Machine Learning; MM/PBSA; Density Functional Theory; Transcriptomics; Multitarget Drug Discovery

Findings

Tauopathies are neurodegenerative disorders caused by dysregulation of the microtubule-associated protein tau (MAPT), leading to hyperphosphorylation, detachment from microtubules, and aggregation into neurofibrillary tangles (NFT). This study aimed to identify tau hyperphosphorylating kinases and potential inhibitors against them for therapeutic development against tauopathy-associated neuroinflammatory diseases.

Microarray analysis of seven GEO datasets spanning 14 brain subregions revealed clear separation between control and disease groups in the hippocampus, entorhinal cortex, and frontal cortex. Protein-protein interaction network analysis of 870 shared significant genes, combined with literature review, identified DYRK1A, ABL1, and TTBK1 as consistently upregulated priority therapeutic targets. DYRK1A primes tau at Thr212 for further hyperphosphorylation by GSK3β, ABL1 links oxidative stress and amyloid toxicity to cytoskeletal collapse via Tyr394 phosphorylation, and TTBK1 phosphorylates Ser422 to drive tau pre-tangle formation.

Structure-based virtual screening of the ZINC12 natural compound database identified ZINC08623207 and ZINC08790347 as ABL1 inhibitors, ZINC04028452 and ZINC08790347 as TTBK1 inhibitors, and ZINC08300244 and ZINC08964763 as DYRK1A inhibitors, all validated through ADMET profiling, DFT calculations, and microsecond-scale molecular dynamics with MM/PBSA analyses. Experimental studies further validated baicalin and thymol as DYRK1A inhibitors, showing strong binding affinity and ATPase inhibition (IC_{50} of 20.01 μM and 39.8 μM respectively) with stable interactions confirmed in silico.

Finally, an ensemble machine learning strategy combining CatBoost, SVM, and XGBoost classifiers (AUROC greater than 0.97) screened approximately 695,000 natural product structures from the COCONUT 2.0 database, identifying CNP0591834.1 and CNP0484145.0 as multitarget inhibitors of DYRK1A, ABL1, and TTBK1. These compounds showed stable binding across all three kinases, establishing a scalable, integrated computational-experimental pipeline for identifying single- and multitarget natural inhibitors against tau hyperphosphorylation-mediated neuroinflammatory diseases.