Fixing rogue brain cells may hold key to preventing neurodegeneration

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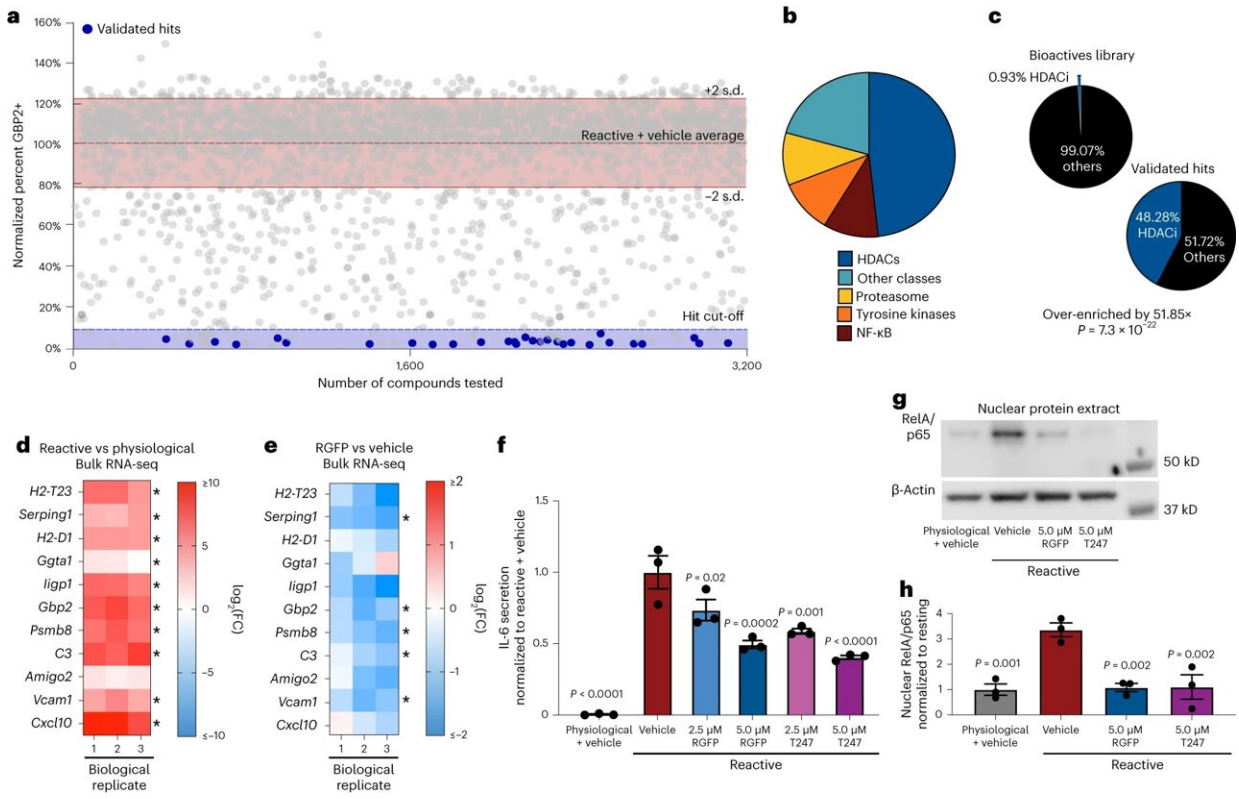

Phenotypic screen identifies HDAC3 as a regulator of pathological reactive astrocytes. **a**, Scatter plot of primary screen results displayed as percent GBP2 positive, normalized to reactive astrocyte plus vehicle controls for all nontoxic chemicals. Validated hit chemicals colored in blue. The dashed blue line represents the hit cut-off at a ≥90% decrease in GBP2-positive astrocytes compared to reactive astrocyte plus vehicle controls. The dashed red line represents the average percent GBP2 positive for reactive astrocytes plus vehicle set at 100%. Solid lines represent ±2 s.d. from the mean of reactive plus vehicle control wells. **b**, Pie chart depicting the chemical class breakdown of all 29

validated chemical hits. **c**, Pie charts depicting the frequency of HDAC inhibitor compounds enriched in the primary screen validated hit list compared to the primary screen chemical library as a whole, showing that HDAC inhibitors are significantly enriched in the validated hit list. *P* value generated by a two-tailed hypergeometric test. **d**,**e**, Heatmap of the $\log_2$(FC) from bulk RNA-seq analysis of reactive versus physiological (**d**) and RGFP966 (RGFP) versus vehicle (DMSO) treated reactive astrocytes (**e**). Red is upregulated and blue is downregulated. Data are presented as $\log_2$(FC) for $n = 3$ biological replicates with asterisks denoting a *P*