- **Methods and protocols**

1. *Nuclei isolation and histone extraction*

After 24h of pesticide treatment, samples consisted of 3 treated vs non-treated brain tumor spheroids were harvested, pooled in a centrifuge tube, washed twice by cold PBS at 4°C, centrifuged at 2500 rpm for 10 min, then collected and lyophilized by a freeze-dryer (CHRIST). Afterwards, the cells were lysed by RIPA Lysis buffer (50 mM Tris–HCl, pH 7.4, 150 mM NaCl, 1% triton X-100, 5 mM EDTA pH 8.0) containing 1× protease inhibitor cocktail (HALT, Thermo scientific), and phosphatase inhibitor cocktail (1 mM NaVO4, 50 nM NaF) (Thermo Scientific), sonicated, then centrifuged at 12,000 rpm for 15 min at 4°C. Subsequently, to each cell pellet which is the nuclear fraction, we added to a ratio of 10:1, a freshly solution of the NIB containing inhibitors at the final concentration of 1mM DTT, 500 µM AEBSF; 5 nM microcystin and 10 mM sodium butyrate, with 0.3% NP-40 alternative that was previously prepared in the solution of NIB with inhibitors.

We mixed cell pellets by gentle pipetting, then incubated on ice for 5 min. We pelleted the nuclei at 600 × g for 5 min, at 4°C. The resulting nuclear pellet was washed twice by NIB containing inhibitors without NP-40 detergent at 10:1 volume ratio. We pelleted again nuclei at max speed (15,000–21,000 × g) for 5 min at 4°C, then we proceeded promptly for acid extraction by re-suspending in 0.4 N H_2SO_4 at 10:1 volume, and incubated at 4°C for 2h on a rotator. We centrifuged extracts at 3400 rcf, 4°C for 5 min, then recuperated the supernatant containing the histone proteins in new eppendorf (EP) tube. Afterwards, histone proteins were precipitated on ice for 1h by adding 100% TCA to the acid extraction supernatant for a final concentration of 20%, then incubated and centrifuged at 3400 rcf for 5min. We aspirated the supernatant, and washed the precipitated protein pellet once with 0.1% HCl in acetone (-20°C), then twice with 100% acetone (-20°C) by pipetting gently down the side of the tube. Next, we centrifuged at 3400 rcf for 5 min, and aspirated acetone. We resuspended the histone film in the ultrapure water, then centrifuged at 3400 rcf for 2 min, and recuperated the supernatant into new EP tube. The final product of this protocol is a highly enriched mixture of histone proteins, which their concentration was determined by a Bradford assay.

2. *Derivatization and digestion*

Samples were dried in a vacuum centrifuge, then resuspended in 100 mM ammonium bicarbonate (pH 8). We proceeded first to the derivatisation of histone proteins on the ξ- amino groups of lysine residues by using propionic anhydride: isopropanol in a 1:3 ratio to generate

longer peptide. Subsequently, we added 5 µl of ammonium hydroxide to set pH 8, then samples were incubated for 15 min at 37°C. After incubation, samples were dried in a vacuum centrifuge to remove propionic acid. We repeated derivatization reaction once, then samples were dried to less than 10 µl of volume, after which re-suspended in 100 µL of 50 mM ammonium bicarbonate (pH 8) and digested by free trypsin at a ratio of 1 µg trypsin:20 µg sample for overnight (16h) at 37 °C. After the trypsin digestion, samples were dried in a vacuum centrifuge, then re-suspended in 20 µL of 100 mM ammonium bicarbonate, pH 8. Finally, the extracted peptides were lyophilized to near dryness, then resuspended in 20 µL of 0.1% formic acid for LC-MS/MS analysis.

3. Analysis by nanoflow UHPLC-MS/MS

Samples were analyzed in the same day by high resolution tandem mass spectrometry consisted of an Ultimate 3000 nano-Ultra-high performance Liquid chromatography (UHPLC) system (ThermoFisher Scientific, USA), an ESI nanospray source, a Q Exactive HF mass spectrometer (Thermo Fisher Scientific, USA), and a higher energy collision induced dissociation (HCD) fragmentation mode. The nano-column comprised of a trapping column (PepMap C18, 100Å, 100 µm × 2 cm, 5 µm) and an analytical column (PepMap C18, 100Å, 75 µm × 50 cm, 2 µm). The loaded sample amount was 1 µg, and the total flow rate was 250 nL/min. The mobile phase consisted of solvent A (0.1% FA in water) and solvent B (0.1% FA in 80% ACN) by linear gradient: from 2 to 8% buffer B in 3 min, from 8% to 20% buffer B in 56 min, from 20% to 40% buffer B in 37 min, then from 40% to 90% buffer B in 4 min.

The full scan was performed between 300-1650 m/z at the resolution 60 000 at 200 m/z. The automatic gain control target for the full scan was set at 3e6. The MS/MS scan was operated in Top 20 mode using the following settings: resolution 15 000 at 200 m/z; automatic gain control target 1e5; maximum injection time 19 ms; normalized collision energy at 28%; isolation window of 1.4 Th; charge state exclusion: unassigned, 1, > 6; dynamic exclusion 30s.

4. Data-MS/MS analysis and histone isoforms identification

Raw MS files were analyzed and searched against a human protein database based on the species of the samples using the MaxQuant (V.1.6.1.14, RRID: SCR_014485) search engine.

The setting parameters were as follows: N-terminal propionylation as a statistic modification ; lysine propionylation and methionine oxidation as variable modifications. The enzyme specificity was set to trypsin and up to two missed cleavages were allowed. The precursor ion mass tolerance was 10 ppm, and the MS/MS fragment ion tolerance was 0.6 Da.

Proteins were identified with high confidence interval at 95%, containing at least one identified peptide. The proteome profiles between the two groups were compared using a false discovery rate (FDR) ≤0.05 as the threshold to judge the significance in protein expression maps difference. Only proteins identified at three times were considered. Proteins were filtered into two categories namely "up-regulated" with positive values, and "downregulated" with negative values based on the $\log_2$ fold change (FC) criteria and by using the paired t-test with a *P* value threshold of 0.05. Scaffold (version 4.10.0, Proteome software, Inc., Portland, OR) was used to validate the MS/MS based peptide and protein identification.

Histone-isoform peptides were reanalyzed by *De novo* peptide sequencing using the "*PEAKS STUDIO*" software package (the latest version 12.5). The latter assigns a local confidence score to each amino acid in a *de novo* sequence, ranging between 0 to 99%, to reveal how confident the algorithm considers a particular amino acid residue to be the correct assignment. Each peptide sequence is evaluated by an ALC score, known as the average of the local confidence scores of all amino acids in the sequence. This ALC score threshold was fixed to filter out the incorrect residues and yielded only the sequences having the same spectral quality as the MS/MS spectra matched confidently the database search.