**Samples preprocessing.**

Minced HCC tissues were lysed in T-PER buffer (Thermo Fisher) containing RIPA-strong and 1xprotease inhibitor, followed by polishing using bead mill. The lysate was centrifuged at 16,000g for 10 min, and the supernatant was collected as whole-tissue extract. Protein concentrations was determined using the BCA assay. The next steps were followed:

1. Take tissue samples, add transient solution (RIPA-strong, 1x protease inhibitor), grind the tissue with a bead grinder, centrifuge at low temperature and high speed at 16000 rpm for 10 minutes and take the supernatant.
2. Determine protein concentration using the BCA assay and proceed with 25 µg protein.
3. Add 1/20 (v/v) 100mM DTT (final concentration is 5 mM) and incubate at 60°C for 30 minutes.
4. Add 1/10 (v/v) 200mM IAM (final concentration is 20 mM) and incubate at RT in the dark for 30 minutes.
5. Quench the reaction by adding 1/20 (v/v) 100 mM DTT and incubate at RT for 15 minutes.
6. Add an optimized amount of prepared beads to the solution (Protein: beads=1:10, i.e., 2µL 50 µg/µL beads for 10 µg of protein).
7. Add equal volume of 100% ethanol to the mixture and incubate the binding mixture in a ThermoMixer at 24 °C for 10 min at 1000 rpm.
8. Remove and discard the unbound supernatant. Wash the beads with 180 µL of 80% ethanol for four times.
9. Add 100 µL of 100 mM ammonium bicarbonate containing trypsin (1:50 ratio of protein to substrate (w/w)) and sonicate the tube for 30s in a water bath.
10. Incubate the digestion for 18h at 37°C in a ThermoMixer at 1000 rpm mixing.
11. Add TFA to a final concentration of 0.1% and centrifuge the tube at 20000g at 24°C for 1 min and keep the supernatant.
12. Freeze dry the sample and resusspend it in 30 µL of 0.1% FA for LC-MS/MS analysis, inject volume is 2 µL.

**LC-MS/MS analysis for WL-2023**

The mass spectrometer was operated in the data-dependent acquisition mode using the Xcalibur 4.1 software and there is a single full-scan mass spectrum in the Orbitrap (350-1800 m/z, 60,000 resolution) followed by 20 data-dependent MS/MS scans at 30% normalized collision energy. The AGC target was set as 2e5, and the maximum injection time was 30 ms. Each mass spectrum was analyzed using the Thermo Xcalibur Qual Browser and Proteome Discoverer for the database searching. Flow rate was 300 nL/min and Chromatography gradient was respectively 0-1.8min(1%-4.5%B), 1.8-2.3min (4.5%-7%B), 2.3-92min(7%-23%B), 92-122min(23%-35%B), 122-123min (35%-55%B), 123-124min (55%-95%B), 124-135min(95%B)

**LC-MS/MS analysis for WL-Fast**

For LC-MS/MS analysis, the peptides were separated by a 39 min gradient elution at a flow rate 0.300 µL/min with the Thermo EASY-nLC1200 integrated nano-HPLC system which is directly interfaced with the Thermo Q Exactive HF-X mass spectrometer. The analytical column was a home-made fused silica capillary column (75 µm ID, 250 mm length; Upchurch, Oak Harbor, WA) packed with C-18 resin (300 A, 3 µm, Varian, Lexington, MA). Mobile phase A consisted of 0. 1% formic acid and mobile phase B consisted of 100% acetonitrile and 0.1% formic acid. The mass spectrometer was operated with a single full-scan mass spectrum in the Orbitrap (350-1800 m/z, 120,000 resolution) . Each mass spectrum was analyzed using the Thermo Xcalibur Qual Browser and Proteome Discovery for the database searching.Flow rate was set as 300 nL/min and chromatography gradient was respectively 0-3min (1%-4.5%B), 3-26.5min (4.5%-25%B, 26.5-30min(25%-3%B), 30-33min(37%-55%B), 33-36min(55%-95%B), 36-39min(95%).

**PXD006512**

The DDA-MS was performed using a nanoflow high performance liquid chromatography system (Easy nLC1000 System, Thermo Fisher) coupled with an Orbitrap Fusion mass spectrometer (Thermo Fisher Scientific, USA) equipped with a source of Nano-ESI (Thermo Fisher Scientific). A 78-minute gradient with a flow rate of 350 nl/min was employed for separation, using buffer A (0.1% formic acid in water) and buffer B (0.1% formic acid in acetonitrile). The collision energy used for each sample experiment was set at 32%. Additionally, during the full MS scan, the AGC target value was set to 5e5, the scan range was 300-1400 m/z, the resolution was set at 120,000, and the maximum injection time was 50 ms.

**PXD002171**

The DDA-MS was performed using an LTQ Orbitrap Elite mass spectrometer (Thermo Scientific, Bremen, Germany) coupled with an Ultimate 3000 RSLCnano system. Unlabeled analysis was conducted using buffer A (0.1% formic acid) and buffer B (0.1% formic acid, 84% acetonitrile) for peptide elution from the analytical column. A gradient from 5% to 40% of buffer B was achieved in 98 minutes at a flow rate of 400 nl/min. Full MS scan spectra were acquired in profile mode on the Orbitrap analyzer at a resolution of 60,000. The scan range was set from 350 to 2000 m/z. The collision energy used for each sample experiment was 35%.

**PXD021797**

The DIA-MS was primarily performed using a Orbitrap Fusion Lumos Tribrid mass spectrometer (Thermo Fisher Scientific, MA, USA) equipped with a Nano-ESI source. Initially, two microliters of peptides were loaded onto an analytical column (Acclaim PepMap C18), and a 120-minute gradient ranging from 3% to 30% of 0.1% formic acid was used for separation.