**Highlights:  85 characters (including spaces) from *Cell* journal**

Linkage disequilibrium analysis identified genome-wide methylation haplotype blocks

Methylation haplotype block shown significantly epigenetic regulatory functions

Methylation haplotype load reflect methylation level and complexity simultaneously

Methylation haplotype load have powerful distinguish ability to tissues and layers

Deconvolution analysis to MHL shown higher tumor component in cancer plasma

Tissue-specific MHBs provide accurate tumor-of-origin mapping for cancer plasma

**Key points: without limitation to the character**

Linkage disequilibrium analysis identified genome-wide methylation haplotype blocks and Methylation haplotype block shown significantly overlapping with traditional epigenetics epigenetic elements indicating potential biological function.

Methylation haplotype load could play as powerful metric to measure the methylation level and methylation complicity simultaneously.

Tissue specific and layer specific methylation haplotype regions were identified and shown powerful distinguish abilities.

Deconvolution analysis shown abundant contribution from WBC in both cancer and normal plasma while tumor-component have higher contribution in cancer plasma compared with normal plasma.

Tissue-specific MHBs based tumor-of-origin prediction provide quite accurate mapping performance compared with traditional prediction model.

Meanwhile, MHB based tumor-of-origin prediction performed better than 5mC based prediction

**Summary**