signatures, with 58% of the complexes exhibiting nonrandom TPCA signatures in at least one of the cell lines profiled. Membrane-embedded complexes are included in CORUM but are likely not amenable to the protocol adopted in this work (*13*). Nonsignificant TPCA signatures could arise for protein complexes with very low interaction stoichiometry—increased assembly can be monitored by changes in TPCA signature. TPCA profiling suggests that many complexes can remain intact yet thermally destabilized in the absence of interaction with DNA and LMW ligands such as ATP (Fig. 2, A and E). We observed many mitochondrial proteins that seem more temperature-resistant in intact cells, as observed previously (*11*). It is unclear whether TPCA is intrinsic and captured by the recent limited proteolysis and MS methodology (*38*).

We observed many more complexes with significant TPCA signature in cells than in lysates, suggesting that TPCA could potentially aid the intracellular studies of weak or transient protein-protein interactions that are not preserved in lysate, including protein complexes that depend on the integrity of chromatin-DNA, membrane, and associated structures for stability. TPCA could be used to validate complexes identified by other proteome-wide methodologies and help in their functional characterization across different cell states and conditions. TPCA also permits studying chemical modulators of protein complexes and interactions directly in nonengineered cells and tissues. Analogous to quantifying expression of genes and proteins from a reference genome and reference proteome, respectively, we envisage TPCA-based profiling with reference interactomes as a system-wide discovery strategy for modulated cellular processes. The method therefore can facilitate the discovery of protein complexes involved in diseases, some as potential therapeutic targets or, by TPCA profiles in patient tissue samples, for prognosis of disease progression or optimization of therapy.

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SUPPLEMENTARY MATERIALS

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Materials and Methods
Supplementary Text
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