題名:Three Dimensional Dissection of Therapeutic Resistance in Breast Cancer.

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摘要:The presence of progesterone receptor (PR) in estrogen receptor (ER)-positive breast cancer is associated with a good prognosis, and indicates that tumors are likely to respond to tamoxifen. However, ER+/PR- tumors respond less well. To reveal the potential molecular mechanism of this phenomenon, we sought to identify differential protein abundances between invasive ductal carcinoma cells from cryopreserved ER+/PR+ and ER+/PR- mammary tumor specimens. Because current proteomics methods are hampered in the examination of most primary human tumor samples by the extreme tissue heterogeneity, we used laser capture microdissection (LCM) to isolate tumor cells and developed a sample pooling strategy to analyze small sample protein lysates. Proteins from LCM-harvested tumors were pooled into four sub-pools from each condition of three tumors/sub-pool, and proteins from respective paired sub-pools were co-electrophoresed by 2-DE using 54-cm IEF over pH 4-9. Abundance ratios were accurately quantified by a differential multiplex radioactive ProteoTope method at low attomole levels (approximately 3.6 microg protein per labeling reaction, <180 ng per multiplex protein sample per 54-cm gel). Applying this approach, differentially displayed proteins were identified by MS using comigrating non-radioactively labeled tumor proteins. They include decreased cytochrome b5 and transgelin, and more abundant CRABP-II, cyclophilin A, Neudesin, and hemoglobin in ER+/PR+ tumors versus ER+/PR- providing a possible explanation for differential susceptibility

against tamoxifen as a result of deregulated cytochrome b5-dependent metabolism. This study demonstrates the potential of ProteoTope and LCM to enable extremely sensitive and precise differential analyses from well-defined primary clinical specimen.