Using Gene Expression Analysis to Identify Tumor Evolution across Cancer Types

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Despite extraordinary efforts to profile cancer genomes, interpreting the vast amount of genomic data in the light of cancer evolution remains challenging. In malignancies we identified as evolving neutrally, clonal selection seemingly occurred before the onset of cancer growth and not in later-arising subclones, resulting in numerous passenger mutations that are responsible for intratumoral heterogeneity. Reanalyzing cancer sequencing data within the neutral framework allowed the measurement, in each patient, of both the in vivo mutation rate and the order and timing of mutations. This result provides a new way to interpret existing cancer genomic data and to discriminate between functional and non-functional intratumoral heterogeneity. Under neutral growth, fundamental parameters describing cancer evolution that have been thus far inaccessible in human tumors, such as the mutation rate and the mutational timeline, become measurable. Notably, this approach also allows the identification of non-neutral malignancies in micro environmental niches may have a strong role during cancer growth. This realization means that the in vivo mutation rate per division and the mutational timeline--factors that have a key role in cancer evolution, progression and treatment resistance--can be measured directly from patient data. These measurements may be useful for the prognostication and personalization of cancer therapy and treatment.

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