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2. Title
   Elucidation of Dynamics of Genome Heterogeneity in Cancers by Long-Term Multiscale Cell Tracking

3. Period
   2021-2024

4. Summary
   In this study, we investigated the dynamic processes and consequences of genomic heterogenization caused by mitotic failure, which has a dual effect on cancer formation and suppression. Long-term cell lineage tracing using live imaging revealed that a single mitotic failure triggered chronic mitotic instability over multiple generations, resulting in a progressive chromosome instability. Transomics analyses of several polyploid subclones generated through mitotic failure revealed that a single mitotic failure triggered diverse and progressive genomic copy number aberrations in the cell population, leading to heterogeneity in gene regulatory states and phenotypes related to cancer pathology, such as cell proliferation and drug resistance. On the other hand, a compound screen identified CENP-E as an inhibitory target that selectively suppressed proliferation of polyploid cells regardless of their karyotypic features. These results provide insight into the key genetic factors causing cellular phenotypic changes through genomic heterogeneity and suggest potential interventions that can overcome heterogeneity. Furthermore, analysis of zebrafish models revealed a mechanism by which the effects of genomic heterogeneity caused by mitotic failure are dramatically mitigated in a spindle checkpoint-dependent manner, avoiding lethal damage to the organism. In the future, detailed cell tracing *in vivo* will reveal how such adaptive regulation at the organismal level breaks down and initiates the progression of cancer pathology.