Degeneration of Mitosis:
Implications to Precision Medicine for Cancers

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Anti-mitosis has been a key strategy of anti-cancer therapies, targeting at a fundamental property of cancer cells, their non-controllable proliferation due to overactive mitotic divisions. For improved anti-cancer therapies, it is important to find out whether cancer cells can proliferate independent of mitosis and become resistant to anti-mitotic agents. In this study, live-cell imaging was applied to both primary-cultures of tumor cells, and immortalized cancer cell lines, to detect aberrant proliferations. Cells isolated from various malignant tumors, such as Grade-III hemangiopericytoma, atypical meningioma, and metastatic brain tumor exhibit distinct cellular behaviors, including amoeboid sequestration, tailing, tunneling, nucleic DNA leakage, as well as prokaryote-like division such as binary fission and budding-shedding, which are collectively referred to and reported as 'non-mitotic proliferation' in this study. In contrast, benign tumors including Grade-I hemangiopericytoma and meningioma were not obvious in such behaviors. Moreover, when cultured in medium free of any anti-cancer drugs, cells from a recurrent Grade-III hemangiopericytoma that had been subjected to pre-operation adjuvant chemotherapy gradually shifted from non-mitotic proliferation to abnormal mitosis in the form of daughter number variation (DNV) and endomitosis, and eventually regular mitosis. Similarly, when treated with the anti-cancer drugs Epirubicin or Cisplatin, the cancer cell lines HeLa and A549 showed a shift from regular mitosis to abnormal mitosis, and further to non-mitosis as the dominant mode of proliferation with increasing drug concentrations. Upon removal of the drugs, the cells reversed back to regular mitosis with only minor occurrences of abnormal mitosis, accompanied by increased expression of the stem cell markers ALDH1, Sox. Oct4 and Nanog. The present study revealed that various types of malignant, but not benign, cancer cells exhibited cellular behaviors indicative of non-mitotic proliferation such as binary fission, which was typical of prokaryotic cell division, suggesting cell level atavism. Moreover, reversible transitions through the three modes of proliferation, i.e., mitosis, abnormal mitosis and non-mitosis, were observed when anticancer drug concentrations were grossly increased inducing non-mitosis or decreased favoring mitosis. Potential clinical significance of non-mitotic proliferation in cancer drug resistance and recurrence, and its relationship with cancer stem cells are worthy of further studies.