

Fight tumor heterogeneity

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Editorial

Intratumor heterogeneity has attracted more and more attention in recent years. Heterogeneity is the driving force of tumor clone evolution [1]. Chromosomal instability, somatic mutation, epigenetic modification and extrachromosomal DNA (ecDNA) contribute to tumor heterogeneity [2,3]. The degree of such heterogeneity is extremely high. Tumors in the same patient, or even cells within the same tumor might exhibit distinct genomic and biological features. Tumor heterogeneity is dynamic as well. In the process of disease progression and even drug treatment, tumor heterogeneity is still expanding [4,5].

Tumor heterogeneity generates a large repertoire composed of distinct tumor cell clones. Each cell clone may respond differently to therapy. Some clones may be insensitive to certain drugs and difficult to be killed by these drugs. Moreover, after a certain drug treatment, tumor cell clones that are sensitive to the drug were killed, while those clones that are insensitive to the drug survive. Through such selection, tumor clones are able to evolve and escape the anti-tumor effect of immune system and show drug resistance [6]. The dynamic feature of tumor heterogeneity provides continuous supply for such selection. Therefore, malignant tumor has been a nerve-cracking thing to clinic doctors for years.

Based on the above knowledge, it is realized that malignant tumor therapy needs personalized precise medicine. With the development of molecular biology and new technologies such as next-generation sequencing, personalized therapy for malignant tumor patients becomes feasible [7]. Several strategies have been proposed to fight tumor heterogeneity as described below:

So far it is yet impossible to completely correct the mutations or change the abnormal epigenetic modifications in tumor cell genome. Tumor clone evolution is hard to be stopped either. However, it is feasible to monitor heterogeneity progression, and respond promptly to adjust the therapeutic regimen. Tissue biopsy is one of the major methods to monitor tumor progress. Biopsy samples should be collected both from different areas of the tumor, and at different time points in the process of tumor development. Sequencing of the DNA from circulating tumor cells (ctDNA), which is known as liquid biopsy, can detect the changes in tumor cell genome prior to medical imaging findings [8]. This is highly beneficial to patients as early detection of tumor clone evolution makes it possible to eradicate recurrent tumor cells before they grow up and metastasize. It should be noted that early detection of tumor clone evolution requires sensitive and reliable detection techniques to be developed.

A feature of tumor genome is chromosomal instability [9]. It makes the tumor genomic DNA easy to mutate. Chromosomal instability accelerates the expansion of tumor heterogeneity repertoire [10]. Attenuating chromosomal instability may slow down the speed of mutation and tumor clone evolution, which will reduce the capability of tumor cells to survive after various treatments. However, few drugs that help stabilize chromosome are available.

It is very hard to eradicate all tumor cells. Alternative anti-tumor strategies emerge. It is found that the characteristic of extensive and rapid mutation also brings weakness to tumor cells. For those genes important for cells, another back-up gene has been reserved, to keep the cell survive when the crucial gene loses its function. This is the consequence of biological evolution. When an important gene in cells is mutated, these cells become very dependent on the back-up gene to survive. For tumor cells with a certain mutant gene, drugs targeting the back-up gene may cause these cells to

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die. This phenomenon is called synthetic lethality [11]. Treatment of BRCA mutant breast cancer with PARP inhibitors is a good example of synthetic lethality strategy [12]. Tumor cells harboring many mutated genes may have many corresponding back-up genes, which are potential targets for drug development. However, it is a great challenge to identify those putative back-up genes and the relevance between the mutant gene and the back-up gene [13]. This depends on our better understanding of the gene functions and the development of bioinformatics analytical method on big data.

All the therapy depends on drug repertoire. The more available drugs, the more choices can be provided to doctors. Quite a lot of drugs have been available, but the drug repertoire is still far from enough, considering the extensive and complicated mutations in tumor cells. No matter by which method the drug is discovered, the action mechanism of the drug should be clearly understanding. Drug development requires long-term and substantial basic research.

Expectation of curing malignant tumor with a single drug seems improbable. Combined therapy is necessary for personalized precise medicine. The detailed therapeutic regime for each patient should be carefully designed and fine-tuned [14]. For example, if multiple drugs are used, some drugs can be used simultaneously, while others are better to be taken sequentially. The progress of tumor clone evolution is necessary to be monitored periodically, which will facilitate the adjustment of therapeutic regime. The toxicity induced by combined multiple drugs should be carefully monitored as well.

Tumor therapy is a complicated system that combines basic research and clinic therapy. It is a typical example of how basic research benefits clinic (bench to bed). It requires the close cooperation not only between scientists and doctors, but also between biological scientists and computational scientists. As the development of new drugs is costly and thus anti-tumor drugs are very expensive, the joint effort of the whole world is required to reduce the financial burden of patients. With the extension of knowledge about tumor heterogeneity and development of new techniques in molecular biology, cell biology, immunology, and big data analysis, it is believed that significant progress will be made in future for malignant tumor therapy.

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