Editorial

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Understanding metabolic reprogramming in tumor microenvironment

https://doi.org/10.1515/mr-2021-0037

Cancer ranks as a leading cause of death and is a most important barrier to increasing life expectancy in the world. There were estimated 19.3 million new cases and 9.6 million cancer deaths worldwide in 2020. China accounted for 24% of newly diagnosed cases and 30% of the cancer-related deaths worldwide in 2020 [1]. In the past decade, tumor immunotherapy, especially the immune-checkpoint blockade (ICB), has achieved a remarkable success. However, a majority of the patients still cannot benefit from the immunotherapy [2]. By recircuiting immunosuppressive cells, building up extracellular matrix and regulating the metabolism circles, tumor cells reshape the tumor microenvironment (TME) to be a hotbed for tumor to develop and resist to antitumor immunity [3]. It has been a challenge to meticulous sketch the cell-cell communication network in TME. Currently, the genomics-based studies have made great achievement, paving the road to understand the complexity of TME. In the current issue, several excellent scientists collaboratively summarize the advance of basic cancer research from different perspectives, from cancer metabolic reprogramming to tumor microenvironment and novel therapies, as well as the advanced sequence technology. Although focused on distinct research fields, most of these reviews highlight the importance of metabolic reprogramming throughout cancer evolution and in TME interactions. Metabolic reprogramming becomes an emerging hallmark of cancer [4, 5]. In total, the progress in understanding the "circulation language" between cancer cells and TME will help us to finally win the war with cancers and improve millions of patient survive.

Genomics based approaches to studies of cancer cells and cancer microenvironment

Recent genomic studies of cancer have greatly advanced our understanding of the underlining basis of this common disease, thus having led to the improvement of cancer treatment and public health over the past few decades. A major force of these discoveries has relied largely on the development of new sequencing technologies and novel computational approaches. In this issue, we have covered reviews in a wide range of such approaches to studies of cancer genomics, including next generation sequencing (NGS), third-generation sequencing (TGS), basic sequence alignment algorithm, and genome-wide association studies (GWAS).

The next-generation sequencing has made DNA sequencing dramatically simpler and faster. The sequencing process uses various platforms, such as DNA sequencing, RNA sequencing (RNA-Seq), single-cell RNA and DNA sequencing. To date, NGS has become a standard tool for many basic biology as well as for clinical and agronomical studies [6]. However, the read length in NGS data remains a bottleneck for biological research. Chen et al. give a brief description of NGS in cancer research, outline the limitations of NGS and then present a comprehensive review of key applications of third-generation sequencing (TGS) in cancer research including the identification of complex structure variation, alternatively splicing, gene fusion, and exogenous RNA [7]. With the technical improvement in reducing sequence errors and the development of novel bioinformatic algorithms, TGS is becoming a complementary sequencing technology alongside with NGS in cancer studies [8, 9].

Genomic signature profiling represented by k-mers is a critical approach to decoding important information from sequencing data. Existing fundamental techniques such as sequence alignment, RNA-seq transcriptome quantification, and microbial community profiling [10] predominantly rely on fixed-size k-mers while many research

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studies have shown the benefits of considering variable-length k-mers. Ju et al. present a novel genomic signature profiling approach, TahcoRoll, by extending the Aho-Corasick algorithm for profiling variable-length k-mers [11]. This new algorithm can potentially improve the current fixed k-mer-based computational pipelines.

Large-scale genome-wide association studies (GWAS) have identified hundreds of single-nucleotide polymorphisms (SNPs) associated with susceptibility to common cancers [12, 13]. Wang et al., having reviewed the major discoveries from cancer GWAS, describe methodologies of leveraging genetic risk factors and review the steps for the development and evaluation of risk prediction models [14].

Intratumor heterogeneity is a confirmed major cause of treatment failure and drug resistance in cancer. Single-cell sequencing has the advantages to addresses this issue by identifying subpopulations of cancer cells and immune cells within a single patient.

Metabolic reprogramming is the key interaction between cancer cells and tumor microenvironment

Efforts to uncover the link between tumor cell genetic mutations and tumor progression have been ongoing for several decades. Recently, scientists have discovered that in addition to gene mutations, tumor progression is also regulated by cancer microenvironment. How cancer cells sense and respond to microenvironmental changes is still a key question. It has been identified that cellular metabolism is an important modifier of various epigenetic modifications, such as DNA methylation, histone methylation and acetylation and RNA N6-methyladenosine (m6A) methylation [15]. In cancer cells, metabolic reprogramming driven by the oncogenic alterations can contribute to altered epigenetic modifications. The metabolites can serve as substrates, cofactors or regulators for epigenetic enzymes, thereby leading to changes in DNA, RNA and histone methylation and acetylation, which then promote the development of cancer [16–18]. Wang et al. summarized the abundance of key metabolites affected by metabolic reprogramming plays an important role in dynamically regulating epigenetic modifications in cancer [19]. Tan et al. further predict that most of the cancerous behaviors are the results of the metabolic reprogramming. Cancer cells have simplified their cellular system by mutating and repressing certain cell-polarity genes to revive a lost capability, namely cell cycle activation and progression driven by nutrient concentrations, for survival [20].

TME is highly hierarchical, and consists of tumor cells, endothelial cells, stromal cells and various types of immune cells. In these tumor-infiltrating immune cells, T cells, as well as NK cells, are tumor killing executors and the fundamental components for cancer immunotherapy. Increasingly more evidence has shown that myeloid cells that infiltrate into the tumor microenvironment are important regulator for both tumor cells and anti-tumor immune cells [21]. A better understanding of the diversity and functional roles of different myeloid cell subtypes and of how they are associated with TME remodeling may help to improve cancer therapy. In this issue, Shen et al. summarized the biological functions and therapeutic relevance of tumor-infiltrating myeloid cells, including tumor-associated macrophages, dendritic cells and neutrophils [22]. Specifically, they discussed how the tumor-derived factors and metabolites reprogram myeloid cells and what the functional interactions are between myeloid cells and other cells in the tumor microenvironment [23]. Understanding of the complexity of myeloid biology will pave the path for the development of novel and more effective therapeutics. A commentary in this issue further addressed the heterogenicity of myeloid cells. Wei et al. discussed the recent research article in *Cell*, that made a pan-cancer single-cell transcriptional atlas of human tumor-infiltrating myeloid cells. The single-cell transcriptome work provides valuable insights for understanding the functional heterogeneity and exploring new therapeutic targets [24, 25].

Targeting metabolic reprogramming for cancer therapy

Several bioenergetic metabolic pathways altered in cancer, including glycolysis, TCA cycle, glutaminolysis and fatty acid oxidation, have been investigated as potential drug targets. Drugs that target a variety of metabolic processes have been tested in preclinical cancer models [26]. Wang et al. summarized that several drugs can directly target metabolic enzymes, and others may have a role in inhibiting pathways that are crucial for supplying nutrients to cancer cells. Furthermore, the regulation of immunometabolism as a means of enhancing anti-tumor immunity is a growing area of active research in the field of cancer therapy. Shen et al. summarized that interfering with lipid metabolism represents a particularly attractive approach to enhancing tumor associate dendritic cells-mediated anti-cancer immunity.

In summary, it is now clear that metabolic reprogramming plays an important role in epigenetic modifications, thereby significantly contributing to cancer development. The advances of cutting edge high-throughput platform such as single-cell sequence, third-generation sequencing and computational methods will play important roles in completely uncovering the complexity of metabolic reprogramming interaction in cancer cells and with their microenvironment. Understanding these interactions will greatly promote the development of novel and more effective cancer therapies.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209–49.
2. Duan Q, Zhang H, Zheng J, Zhang L. Turning cold into hot: firing up the tumor microenvironment. Trends Cancer 2020;6: 605–18.
3. Binnewies M, Roberts EW, Kersten K, Chan V, Fearon DF, Merad M, et al. Understanding the tumor immune microenvironment (TIME) for effective therapy. Nat Med 2018;24:541–50.
4. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144:646–74.
5. Pavlova NN, Thompson CB. The emerging hallmarks of cancer metabolism. Cell Metabol 2016;23:27–47.
6. Goodwin S, McPherson JD, McCombie WR. Coming of age: ten years of next generation sequencing technologies. Nat Rev Genet 2016;17:333–51.
7. Chen Z, He X. Application of third-generation sequencing in cancer research. Med Rev 2021;1:150–71.
8. Van Dijk EL, Jaszczyszyn Y, Naquin D, Thermes C. The third revolution in sequencing technology. Trends Genet 2018;34:666–81.
9. Logsdon GA, Vollger MR, Eichler EE. Long-read human genome sequencing and its applications. Nat Rev Genet 2020;21:597–614.
10. Angizi S, Fahmi NA, Zhang W, Pim-assembler DF. A processing-in-memory platform for genome assembly. In: *2020 57th ACM/IEEE design automation conference. (DAC)*. IEEE; 2020:1–6 pp.
11. Ju CJ-T, Jiang J-Y, Li R, Li Z, Wang W. TahcoRoll: fast genomic signature profling via thinned automaton and rolling hash. Med Rev 2021;1:114–25.
12. Torkamani A, Wineinger NE, Topol EJ. The personal and clinical utility of polygenic risk scores. Nat Rev Genet 2018;19:581–90.
13. Chatterjee N, Shi J, Garcia-Closas M. Developing and evaluating polygenic risk prediction models for stratified disease prevention. Nat Rev Genet 2016;17:392–406.
14. Wang Y, Zhu M, Ma H, Shen H. Polygenic risk scores: the future of cancer risk prediction, screening and precision prevention. Med Rev 2021;1:129–49.
15. Saggese P, Sellitto A, Martinez CA, Giurato G, Nassa G, Rizzo F, et al. Metabolic regulation of epigenetic modifications and cell differentiation in cancer. Cancers 2020;12:3788.
16. Xia L, Oyang L, Lin J, Tan S, Han Y, Wu N, et al. The cancer metabolic reprogramming and immune response. Mol Cancer 2021;20:28.
17. Zhao Z, Shilatifard A. Epigenetic modifications of histones in cancer. Genome Biol 2019;20:245.
18. Dai Z, Ramesh V, Locasale JW. The evolving metabolic landscape of chromatin biology and epigenetics. Nat Rev Genet 2020;21: 737–53.
19. Wang G, Han JJ. Connections between metabolism and epigenetic modifications in cancer. Med Rev 2021;1:199–221.
20. Tan R, Zhou Y, Zheng A, Xu Y. Cancer is a survival process under persistent stresses. Med Rev 2021;2. In press.
21. Engblom C, Pfirschke C, Pittet MJ. The role of myeloid cells in cancer therapies. Nat Rev Cancer 2016;16:447–62.
22. Shen M, Du Y, Ye Y. Tumor-associated macrophages, dendritic cells, and neutrophils: biological roles, crosstalk, and therapeutic relevance. Med Rev 2021;1:222–43.
23. Liu PS, Wang H, Li X, Chao T, Teav T, Christen S, et al. α-ketoglutarate orchestrates macrophage activation through metabolic and epigenetic reprogramming. Nat Immunol 2017;18: 985–94.
24. Cheng S, Li Z, Gao R, Xing B, Gao Y, Yang Y, et al. A pan-cancer single-cell transcriptional atlas of tumor infiltrating myeloid cells. Cell 2021;184:792–809.
25. Wei J, Bu Z, Ji J. A commentary on: "A pan-cancer single-cell transcriptional atlas of tumor infiltrating myeloid cells"- tumor microenvironment: the Achilles heel of cancer. Med Rev 2021;1: 126–8.
26. Galluzzi L, Kepp O, Vander Heiden MG, Kroemer G. Metabolic targets for cancer therapy. Nat Rev Drug Discov 2013;12:829–46.