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LETTER TO THE EDITOR

The Pan-Cancer Atlas: a New Chapter in Cancer Molecular Targeting Therapy

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To editor

Conventional treatments for tumor mainly include surgery, chemotherapy and radiotherapy based on different types and pathophysiological processes of tumor. Targeted therapy and immunotherapy are currently restricted by multiple factors including the tumor heterogeneity, although related drugs (e.g., geftinib and pembrolizumab) are gradually emerging [1, 2]. Interestingly, cancers in different organs and tissues have similarities at the molecular level, and their similarity is even greater than that of the same tumors, suggesting the possibility for the precision treatment of tumor [3]. NIH-funded researchers have launched a collaboration called The Cancer Genome Atlas (TCGA) Pan-Cancer project to analyze multiple tumor types from the perspective of molecular characteristics. Recently, the Pan-Cancer Atlas has been mapped and provides a panoramic view of how, where and why cancers arise in humans (consisting mostly of cell-of-origin patterns, oncogenic processes and signaling pathways) [4–6].

The Cancer Molecular Classification

During tumor development, the diversity of genomic aberrations, altered signaling pathways and oncogenic processes is influenced by various factors, including the development, differentiation and epigenetic regulation of carcinoma cells. But, molecular similarities among histologically related cancer types provide a basis for pan-cancer analysis. Integrative clustering of aneuploidy, DNA methylation, mRNA, miRNA, and protein expression data from 11,000 tumor samples across 33 tumor types reveal that cell-of-origin among different cancer types is a prominent feature of the tumor classification [4]. A new 28-clustering of tumor types is applied to reclassify human tumors. The two-thirds of molecular subclassifications show varying degrees of heterogeneity, and the most diverse cluster contains 25 tumor types [4]. The traditional tumor classification organized by histology or anatomic origin should be supplemented by the Pan-Cancer Atlas molecular taxonomy based on molecular similarity shared by tumors across distinct tissue types.

Most of heterogeneous subgroups contain cancer types that fell within four major cell-of-origin patterns: pan-gastrointestinal, pan-gynecological, pan-squamous, and pan-kidney. According to the shared and distinguishing molecular characteristics, GI adenocarcinomas comprise five molecular subtypes. Pan-gastrointestinal tumors with chromosomal instability (CIN) show fragmented genomes, whereas genomically stable (GS) colorectal cancers are enriched in mutations in SOX9 and PCBP1 [7]. Five pan-gynecological tumor subtypes are responsible for unsupervised hierarchical clustering of 16 molecular characterizations [8]. Two of the pan-gynecological subtypes show elevated levels of hormone receptors (ERs, PR/AR high), indicative of possible responsiveness to hormone therapy [8]. Pan-squamous cell cancers (SCCs) from five subsets of squamous cell carcinomas have distinguishing molecular features from other cancers and subclassifying by integrated analyses of genetic and epigenetic alterations [9]. Subtype-specific molecular characterization of renal cell carcinoma (RCC) uncovers relevant somatic mutations within three RCC histologic subtypes including clear cell RCC (ccRCC), papillary RCC (PRCC) and chromophobe RCC (ChRCC) [10]. TP53 mutation is associated with decreased survival in ccRCC and PRCC, BAP1 mutation in ccRCC, and PTEN as well as PBRM1 alteration in ChRCC,

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whereas CDKN2A alteration, DNA hypermethylation and increased immune-related Th2 gene expression are linked to reduced survival in each RCC subtype [10].

The Oncogenic Molecular Processes

The oncogenic processes governing cancer development and progression concentrate on chromosomal-level aneuploidy, splicing events, germline and somatic mutations, and driver gene fusions [5]. Chromosome arm-level alterations display cancer-type-specific characteristics, such as loss of chromosome 3p in squamous cell lung cancer [11]. 1964 mostly splice-site-disrupting mutations lead to alternative splice site creation across 33 tumor types, separated by conventional somatic mutation annotations [12]. Somatic hotspot mutations in splicing factor genes (like SF3B1, U2AF1 and SRSF2) contribute to RNA splicing deregulation in cancer, which may represent an important hallmark of tumorigenesis [13]. Mutations in many predisposition genes, including BRCA1 and BRCA2, take a higher proportion of germline variants than somatic drivers, highlighting the role of genome integrity in tumor susceptibility [14]. Gene fusions, which have the potential to rearrange gene promoters to amplify oncogenic function, often function as diagnostic markers for specific cancer types, such as a fusion between BCR and ABL1 in chronic myeloid leukemia [15]. The most recurrent fusions within any cancer type are TMPRSS2–ERG in prostate adenocarcinoma, and fusion drivers are also present in specific subsets of tumors (e.g., ALK–EML4 fusions in lung adenocarcinoma) [16].

The Oncogenic Signaling Pathways

Signaling pathways are altered in tumor at varying frequencies and in varying combinations across tumor types, suggesting complicated interaction and pathway crosstalk. Certain key signaling pathways, like RTK-RAS signaling, are frequently altered in different types of cancer, while other pathways are altered in small subsets of malignancies (e.g., recurrent alterations of the oxidative stress response pathway in squamous histologies) [17]. Francisco et al. summarized ten canonical cancer pathways, including the cell cycle, Hippo, Myc, Notch, Nrf2, PI3K, RTK-RAS, TGFβ, p53 and Wnt pathway, with frequent genetic alterations from 33 cancer types [6]. The RTK-RAS pathway is the signaling pathway with the highest fraction of alterations (46%) across all cancer types, followed by the cell cycle (45%) and PI3K pathways (33%) [6]. Melanoma is the tumor subtype with the highest frequency (94%) of alterations in the RTK-RAS pathway. Interestingly, the alterations in some pathways (like the cell cycle, PI3K pathway) are disseminated over several genes, while the alterations in others (such as the Wnt, Myc and Nrf2 pathway) mainly affect only a few genes.

Illuminating the mutual exclusivity and co-occurrence of pathway alterations across distinct tumor subtypes is associated with potential therapeutic implications, as the varying frequencies of oncogenic gene alteration. 89% percent of tumors have at least one driver alteration in ten canonical pathways above, and 57% percent of tumors have at least one alteration potentially targetable by currently available drugs, most notably BRCA1/2 and IDH1/2 [6]. Moreover, 30% percent of tumors (e.g., the MSI and POLE subtypes) have two or more targetable alterations, indicating candidate drugs for combination therapy [6]. For example, a combination of CDK4 and MDM2 inhibitors is synergistic in dedifferentiated liposarcomas by the frequent co-amplification (78%) of the two targets [18].

Conclusion

The pan-cancer atlas is a large and systematic research report with a lot of novel discoveries and subversive breakthroughs. New Pan-Cancer atlas reclassifies human tumor types based on molecular similarity, discloses the complex milieu of oncogenic processes, and clarifies the mechanisms and co-occurrence of the genetic alterations in oncogenic signaling pathways. Moreover, it will help to accurately select customized drugs or comprehensive therapy scheme. The Pan-Cancer atlas reveals the common roots of diverse tumors, indicative of opportunities for better informed clinical trials and targeting therapies for cancer.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest.

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