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Precision Oncology: Bridging the Knowledge Gap with Multi-Omics

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Abstract

The newly-established view in cancer management is that "one size does not fit all". Every tumour type is a molecularly unique and complex entity, due to inter- and intra-tumour heterogeneity, not only between patients, but in the same patient as well. Diagnostic and therapeutic strategies should be specifically tailored to each patient, however widely accepted criteria for patient stratification and individualizing treatment are still elusive. Undoubtedly, it is time for oncology to move from basic to translational clinical research and multi-omics strategies can pave the way towards this goal by employing a bench-to- bedside attitude.

Keywords: Omics; Biomarkers; Precision Oncology

Discussion

In spite of the long-standing history of cancer and the breadth of research concerning its diagnosis and treatment, strategies for its effective therapy are still insufficient or lacking. The management of this disease based on molecular and cellular characteristics is still a relatively new notion. Here in, we discuss the current challenges faced in oncology (and precision oncology), how the medical community deals with them so far and we suggest a new way to address these challenges with the implementation of multi-omics strategies in the clinic.

What are the current challenges in oncology?

In conventional oncology, one specific molecular alteration that serves as a biomarker is considered enough to determine the therapeutic course of action (ignoring the complete picture of the tumour). However, tumours act as stand-alone living organisms that adapt to signal changes in their environment (hypoxia, nutrient deprivation, xenobiotics etc.), which subsequently shape their molecular profile. The chaotic molecular landscape that arises (genomic aberrations, transcriptomic, epigenomic, proteomic and metabolic alterations) does not necessarily play a causative role in its entirety, since only a number of molecules may be drivers for the disease while others may be the simple by-products of these changes. Both kinds of molecular alterations, though, seem to trigger a number of pathological events and thus feed the vicious cycle of carcinogenesis. If these complex interactions in biological systems are accurately explored on several levels, the unique signature and behaviour of each tumour is revealed [1-3]. Although the era of precision medicine in cancer is upon us, so far pharmacogenomics has been the only means towards the implementation of personalised treatment in the clinic. Furthermore, the current model for precision oncology usually calls for retrospective changes in the treatment of patients with refractory or late-stage cancer, based on their genomic profile, which in most cases proves to be insufficient for the successful cure of their disease [4-7]. Cancer is a highly heterogeneous condition (both inter- and intra-individually) consisting of complex phenotypes and systems biology, so genomics represents only the tip of the iceberg for the complete profiling of all cancer subtypes. For this reason, there is a lack of large randomized clinical studies that support genomics' usefulness in the successful management of cancer patients. This unmet need is of paramount importance, especially with the advent of innovative and promising new therapies that call for tailor-made decisions, such as immunotherapy and targeted therapies [8,9]. Is precision oncology just a theory or can we employ a different strategy to explore cancer biology and thus add more information to the clinician's toolbox towards its management?

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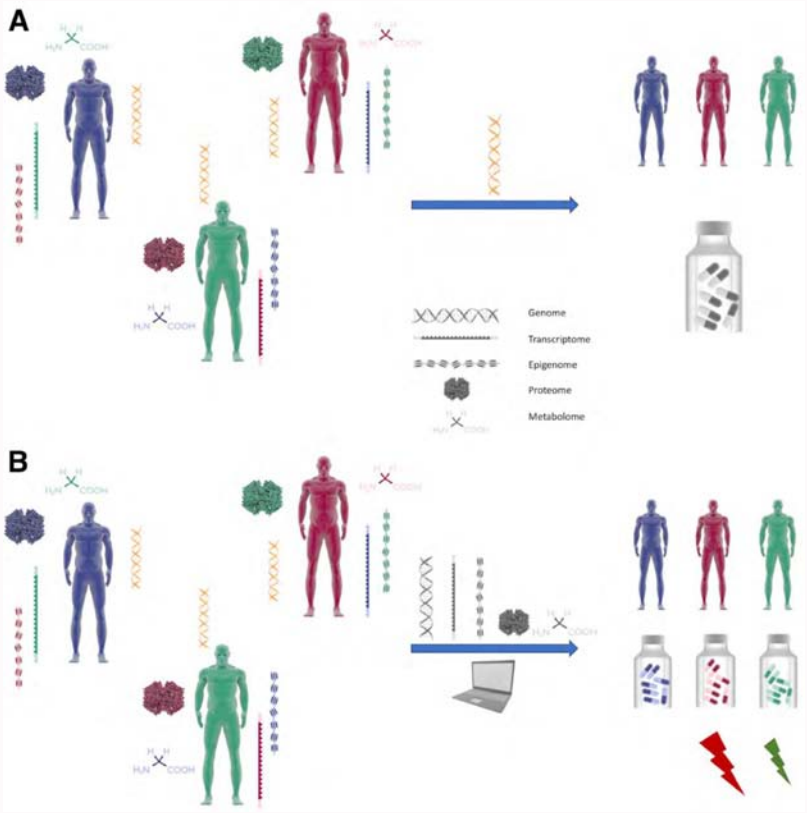

Figure 1: Moving from a traditional drug-centric to a patient-centric approach in precision oncology.
A. In traditional precision oncology, a drug-centric approach is implemented wherein hypothesis-driven molecular alterations stratify patients into broad groups that share the same treatment.
B. In the patient-centric approach, though, the unique molecular profile of each patient is taken into account (comprised of genomic, transcriptomic, epigenomic, proteomic and metabolomic features) which guides their treatment in a tailor-made manner.

How have we dealt with these challenges so far?

Tumour grading so far is mostly dependent on the analysis of light microscopy and immunohistochemical findings. This grading system based on phenotypic characteristics and inadequate hypothesis-driven molecular alterations, results in a broad classification of tumours and does not reflect their unique signatures or their systems biology [10-13]. More importantly, it perpetuates the drug-centric approach to therapy, by grouping together patients that share insufficient common features and treating them with the same modalities, resulting in disappointing outcomes. Instead, we propose a patient- centric approach that takes into account the unique cancer fingerprint of each patient, based on a plethora of molecular, imaging and clinical features in a hypothesis-free and unbiased way to guide their treatment [14]. To support this notion, we have to answer the question on which biomarkers are important in the prognostic or diagnostic evaluation of which cancer types and whether they can offer clinically valuable information to make an evidence-based decision on the right treatment strategy.

Can multi-omics support precision oncology as a new tool?

In the era of precision oncology and Big Data, data generation and data modeling are of paramount importance. Data generation through high-throughput technologies and data modeling with the aid of powerful computational tools for the interpretation of the former in an accessible way can turn information growth into knowledge growth with immense clinical value. For this reason, we propose the implementation of multi-omics strategies (genomics, transcriptomics, epigenomics, proteomics, and metabolomics) and their combinations. In particular, genomics allows for the identification of genes and genetic loci involved in the development of diseases, transcriptomics analyse the gene expression patterns which can inform us on their functional state and epigenomics study the reversible modifications on DNA or histones that can affect gene expression. Proteomics explore the localisation, interactions and conformational changes that proteins undergo under various stressors or time points, while in metabolomics we study the collection of metabolites and their fluctuation that represents the physiological state and behaviour of the cells they are produced by towards intrinsic or environmental stressors [15]. As a whole, these strategies allow for the analysis of raw data on key molecules involved in tumour biology, in order to successfully delineate their impact on disease on multiple levels. Consequently, powerful information technologies and artificial intelligence tools, coupled with pathway analysis software, need to be employed so as to integrate every omics layer and extract statistically significant and biologically functional markers (risk, prognostic, predictive and response biomarkers) that are associated with each individual tumour type. Through this analysis, a comprehensive molecular signature of cancer is anticipated to unfold. Furthermore, the added integration of clinical and imaging datasets with multi- omics strategies and selected end points of interest (such as improved therapeutic outcome, disease-free survival, mortality etc.) will empower biomarker and drug-target discovery through patient and disease stratification [16-18]. The facts claimed above are

Table 1: Studies on breast, lung and colorectal cancer utilizing -omics strategies.

Cancer type	Analytical datasets	Molecular markers	Application	Reference
Breast cancer	transcriptomics, proteomics, metabolomics	Mc1, Mc2, Mc3 metabolic clusters	differential diagnosis	-14
Breast cancer	transcriptomics, epigenomics	High methylated lncRNAs (HMLncs)	prognosis	-15
Triple negative breast cancer	proteomics, metabolomics, subcellular imaging	plasma Homocysteine, DNA damage, SOD, Catalase, Peroxiredoxin, Thioredoxin, RhoA, Actin, Profilin-1, S100A	disease characterization	-16
Non-small cell lung cancer	transcriptomics, proteomics	deregulated abundance of miRNAs, mRNAs and proteins	disease characterization	-17
Lung adenocarcinoma	genomics, epigenomics, transcriptomics	*NUP210*	diagnosis	-18
Lung adenocarcinoma, lung squamous cell carcinoma	transcriptomics, proteomics	differential protein expression patterns	diagnosis and differential diagnosis	-19
Colorectal cancer	genomics, transcriptomics, epigenomics	relative expression ordering-based signature	prognosis and resistance to 5-fluorouracil-based chemotherapy	-20
Colorectal cancer (left-sided and right-sided)	genomics, transcriptomics, epigenomics	methylation signatures, gene (e.g. *PRCA1*) and miRNA differential expression	differential diagnosis and prognosis	-21
Colorectal cancer	metabolomics	35 metabolites, glycerophospholipids	risk assessment	-22

supported by multiple encouraging findings in the current literature. Taking breast cancer, lung cancer and colorectal cancer as examples for biomarker development with - omics strategies, they can serve as paradigms for other types of cancer (Table 1).

How can multi-omics be implemented in the clinic?

In order for multi-omics to prove their clinical efficiency, large prospective and innovative clinical trials have to be designed. Genomics has proven that traditional clinical trial designs, in which groups of patients are retrospectively given the same treatment, based on their common genomic aberrations, has doubtful results and does not reflect precision oncology as it is currently envisaged [19,21]. Instead, we suggest that every patient is tested prospectively for their universal molecular profile of the tumour at the time or before the diagnosis of cancer. As the unique signature of each tumour unfolds, we expect that different combination treatment regimens will be employed on every patient, which match their molecular fingerprint (Figure 1) [22]. Although we are still a long way from fully understanding tumours' system biology, integrative and cost-effective molecular diagnostic tests with clinically valuable biomarkers that can be used to screen at risk populations need to be developed. Also, predictive, prognostic and response markers that are tested at the time of diagnosis and progression of cancer can further aid clinicians to optimally manage the disease. Liquid biopsies and non-invasive tools such as micro fluidics technology can provide the necessary diagnostic data, while the study of immunohistochemical material may subsequently prove outdated. Furthermore, large curated clinical databases containing these datasets can further support and guide clinical decisions, taking ethical and security issues into account. However, it remains to be proven which groups of people will benefit from these tests in advance.

Conclusion

If precision medicine is envisaged, evidence-based decisions have to be made concerning the right treatment at the right time for the right patient. For a multifaceted disease such as cancer, this is of particular clinical value. Through the delineation of the tumour's biological networks and what pathways are active in carcinogenesis at which point in time, information on its aggressiveness, metastatic potential or resistance to therapies (intrinsic or acquired) is obtained. Taking into consideration cancer's vast heterogeneity, we suggest that the implementation of integrative multi-omics strategies and innovative trial designs is the way forward in our efforts to determine clinical actionable biomarkers. These biomarkers can aid optimal patient stratification and selection of the best suited- candidates who will benefit most from particular treatments.

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