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Feature Review

Precision Oncology: The Road Ahead

Daniela Senft,[1] Mark D.M. Leiserson,[2,6] Eytan Ruppin,[3,4] and Ze'ev A. Ronai[1,5,*]

Current efforts in precision oncology largely focus on the benefit of genomics-guided therapy. Yet, advances in sequencing techniques provide an unprecedented view of the complex genetic and nongenetic heterogeneity within individual tumors. Herein, we outline the benefits of integrating genomic and transcriptomic analyses for advanced precision oncology. We summarize relevant computational approaches to detect novel drivers and genetic vulnerabilities, suitable for therapeutic exploration. Clinically relevant platforms to functionally test predicted drugs/drug combinations for individual patients are reviewed. Finally, we highlight the technological advances in single cell analysis of tumor specimens. These may ultimately lead to the development of next-generation cancer drugs, capable of tackling the hurdles imposed by genetic and phenotypic heterogeneity on current anticancer therapies.

Precision Medicine Aims to Address Inter- and Intratumor Heterogeneity

Precision medicine aims to use multiple types of data to classify patients into groups that will most likely respond to a given treatment. The identification of **biomarkers** (see Glossary) that correlate with response to therapy or function in disease initiation and/or progression (therefore representing therapeutic targets themselves) is fundamental in this process [1]. Determination of molecular biomarkers is not limited to a specific methodology, and DNA, RNA, proteins, metabolites, or microorganisms can individually, or in combination, serve as biomarkers. With cancer primarily being a genetic disease, precision oncology has largely focused on the determination of genetic biomarkers and multiple clinical trials test whether targeting these genetic alterations in cancer can prolong survival. Remarkable success in applying genomics-driven cancer therapy has been noted [2], yet, serious criticism remains regarding this genomics-focused precision oncology concept, including scientific, social, ethical, and economical aspects [2–5]. In this review, we focus on the biological rationale for precision oncology and outline current efforts and achievements of implementing precision oncology in the clinic, while highlighting promising routes to overcome the limitations of genomic-focused approaches. The current availability of screening platforms and the armamentarium of anticancer drugs now allows us to recognize and address **intertumor heterogeneity** (i.e., the different molecular characteristics observed between patients). We outline how the simultaneous assessment of genomic and transcriptomic data, combined with functional testing, can serve to overcome hurdles imposed by intertumor heterogeneity. In addition, we discuss the major limitations of prolonged response to current anticancer therapies, including **intratumor heterogeneity (ITH)**; namely, differences in the molecular make-up of tumor cells within individual patients. We have only begun to decipher and address such challenges therapeutically.

The Technical and Molecular Basis for Precision Oncology

The ability to detect mutations in a tumor sample was one of the first milestones in recognizing the genetic events that underlie the cellular transformation process, denoting an early phase of

Trends

Genomics-driven cancer therapy benefits a subset of patients, although there are clear shortcomings to this approach.

Using genomics as a single 'biomarker' to inform therapy is insufficient to comprehensively predict efficient therapeutic approaches. By providing information about active pathways, the inclusion of transcriptomic data reveals a more comprehensive and, thus, accurate molecular profile, which likely improves the choice of therapy.

Available patient-derived functional models (e.g., organoids or patient-derived xenografts) are promising for testing multiple drugs and/or drug combinations in a clinically relevant time-frame.

Mining available data sets can allow researchers to comprehensively map the processes that drive cancer and reveal novel vulnerabilities.

Intratumor heterogeneity remains one of the biggest challenges in reaching sustained therapeutic responses to cancer treatment. Integrating additional factors (immune, metabolome, and microbiome) could pinpoint novel putative therapeutic approaches and combinational drug therapies, in an effort to overcome tumor heterogeneity.

[1]Tumor Initiation and Maintenance Program, NCI designated Cancer Center, Sanford Burnham Prebys Medical Discovery Institute, La Jolla, CA 92037, USA
[2]Microsoft Research New England, Cambridge, MA 02142, USA
[3]School of Computer Sciences and

 http://dx.doi.org/10.1016/j.molmed.2017.08.003

genetic-based evidence for cancer occurrence and development. Improved technologies enabling the detection of such mutations in non-neoplastic tissues (including bodily fluids) has allowed the early detection of somatic oncogenic mutations, such as Ras mutations and hotspot p53 tumor suppressor mutations [6–8]. While these developments reflect advances made already during the 1980s, it has taken another generation to better establish the importance of mutation frequency, its variability in the transformed tissue, and its causative role. This growing understanding has been a prerequisite for the introduction of mechanism-based therapies into clinical practice. Commonly known as **targeted therapies**, these therapeutic approaches are based on small molecules or monoclonal antibodies that inhibit **oncogenic drivers** [9–14], or target genetic vulnerabilities [e.g., poly (ADP-ribose) polymerase (PARP) inhibitors in tumors with **homologous recombination deficiency** [15]]. Several years of clinical experience with targeted agents, and especially of the resistance to drugs, has led to the recognition of the central role of genetic heterogeneity and plasticity of growth-promoting signaling pathways in determining a patient's individual response. A notable example is the targeting of BRAF mutations, which are present in more than 40% of melanomas [16]. Although targeting recurrent BRAF mutation(s) by mutant-specific BRAF inhibitors demonstrated great clinical success [9,17], understanding the complex feedback and crosstalk between key players of the altered RAS/RAF/MEK/ERK signaling axis became necessary for optimizing therapy. Accordingly, in terms of clinical outcomes, combined BRAF and MEK inhibition proved superior over single-agent use [18]. Furthermore, new generations of specific BRAF inhibitors are currently in the pipeline, finely tuned to overcome mutation-driven altered signaling events in the RAS/RAF/MEK/ERK pathway [18]; these might be expected to outperform previous inhibitors of this pathway. Similar undertakings may be required to target deregulated signaling pathways arising from other mutations in different tumors, where a **driver** mutation is known, and where drugs targeting a given driver may exist.

Beyond direct targeting of genomic alterations, the impact of **differentiation hierarchies**, **epigenetic alterations** and the role of the microenvironment in driving tumor pathogenesis have become increasingly recognized. Accordingly, therapeutic approaches that aim to restore normal differentiation programs, such as all-*trans* retinoic acid in acute promyelocytic leukemia and neuroblastoma, have been developed [19]. Along these lines, drugs are and/or have been developed to reprogram epigenetic marks and restore normal gene expression programs, such as various **histone deacetylase** (**HDAC) inhibitors** [20], in addition to drugs that interfere with tumor–microenvironment crosstalk, including **angiogenesis** inhibitors [21] and immunotherapeutic agents [22].

The search for cancer vulnerabilities in specific cancer types has been facilitated by numerous technological advances yielding large-scale molecular profiling of major cancer types [23,24]. This system-based analysis of tumor samples, together with massive hypothesis-based research, has significantly changed our understanding of cancer biology (Figure 1, Key Figure): carcinogenesis is generally considered to be driven by the natural selection of continuously acquired genetic and epigenetic variation in individual cells [25]. These converge on common phenotypic characteristics for cancer cells, including sustained proliferation, migration, invasion, and/or resistance to apoptosis [26]. Tissue microenvironments provide the fitness selection defining spatial and temporal changes in environmental pressures. These influence the evolutionary path of any given cancer cell, resulting in (epi-)genetically heterogeneous subpopulations. Diversity within cancer cell populations is not limited to the genome, and dynamic variations in differentiation hierarchies, transcriptional signals, and the proteomic landscape add to the **phenotypic heterogeneity** observed within tumors [27]. Indeed, cancer cells do not exist as isolated entities, but rather, engage in heterotypic interactions with stromal cells and cooperate with adjacent tumor subclones; this is important, because it can result in the increased robustness of a tumor [28].

Sackler School of Medicine, Tel Aviv University, Tel Aviv, 69978, Israel
[4]Center for Bioinformatics and Computational Biology, University of Maryland, College Park, MD 20742, USA
[5]Technion Integrated Cancer Center, Faculty of Medicine, Technion, Israel Institute of Technology, Haifa, 31096, Israel
[6]Center for Bioinformatics and Computational Biology, University of Maryland, College Park, MD 20742, USA

*Correspondence:
zeev@ronailab.net (Z.A. Ronai).