Review

Molecularly targeted cancer therapy: some lessons from the past decade

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The tremendous advances achieved in the understanding of cancer biology have delivered unprecedented progress in molecularly targeted cancer therapy in the past decade. The fast growing category of targeted anticancer agents available for clinical use is accompanied by a conceptual revolution in anticancer drug development. Nevertheless, molecularly targeted cancer therapy remains challenged by a high failure rate and an extremely small proportion of patients that can benefit. It is pivotal to take lessons from the past and seek new solutions. This review discusses conceptual progress and remaining challenges in molecularly targeted cancer therapy, and proposes feasible alternatives to increase chances of clinical success in the future.

The past decade has witnessed remarkable advances in the understanding of intricate molecular mechanisms underlying malignant progression of human cancer. This progress has led to some remarkable clinical successes in molecularly targeted cancer therapy, with the development of new compounds that interrupt specific molecular abnormalities driving cancer growth and progression (Box 1, Box 2, and Figure 1). However, despite conceptual advancements in cancer therapy and drug development, targeted cancer therapy is almost inevitably challenged by the occurrence of drug resistance. The response rate to targeted therapy across an unselected patient population is marginal, usually 10–20%. In most cases, clinical responses are short-lived (typically 6–12 months) and are almost invariably followed by disease progression [1–4]. The frequent occurrence of drug resistance reflects our inability to fully exploit the weakness of cancer and urges us to seek new breakthroughs [5]. Genetic studies in particular have highlighted the complex heterogeneity of tumors. In this review, we will discuss challenges stemming from tumor heterogeneity, and how progress in personalized medicines and biomarker discovery may aid in the development of new therapies going forward. We will also discuss innovative preclinical models that are able to faithfully predict clinical outcomes and possess high reliability for biomarker discovery.

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Tumor heterogeneity and drug resistance

Tumor heterogeneity refers to the existence of cell subpopulations harboring distinct phenotypic diversity resulting from the integration of both genetic and non-genetic influences, within (intratumor heterogeneity) and between tumors (intertumor heterogeneity) [6]. Cancers evolve by a reiterative process of clonal expansion, genetic diversification, and clonal selection within the adaptive landscapes of tissue ecosystems [7]. Tumor heterogeneity is believed to stem mainly from a Darwinian-like clonal evolution with genetic instability as an intrinsic driving force [8]. Uncontrolled cell division, which is required for full-blown malignancies, causes higher incidence of genetic instability arising from replication errors and increases opportunities for the emergence of multiple mutants. This genetic heterogeneity translates into phenotypic and functional heterogeneity, leading to coexistence of genetically divergent tumor cell clones. In addition, a substantial fraction of nonheritable phenotypic heterogeneity can arise from differentiation of cancer stem cells and morphological and epigenetic plasticity, driven by the selective evolutionary pressure from microenvironmental cues [6,9]. Together, these explain how spontaneous tumors originate from a single cell, or very a few cells, but end up with startling heterogeneity in morphological and physiological features at the time of diagnosis.

Genetic subtyping of cancers

Recently, increasing appreciation of tumor heterogeneity has aroused interest in understanding its profound implications in determining the outcomes of drug therapy [10,11]. A single cancer type defined by a morphology-based taxonomy [e.g., non-small cell lung cancer (NSCLC)] is now known to carry distinct genetic signatures and growth dependency, and hence exhibits different sensitivity to targeted therapy. Such intertumor heterogeneity is recognized as the key factor accounting for very limited response rate across unselected patients. Thus, efforts to define the molecular subtypes of cancer have gained increasing attention. The newly updated snapshot of NSCLC is a good example. Over 15 genomic subtype signatures, including KRAS, epidermal growth factor receptor (EGFR), phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PI3KCA), PTEN mutations, anaplastic lymphoma kinase (*ALK*), *ROS1* translocations, and

Box 1. Molecularly targeted cancer therapy

Molecularly targeted therapy refers to a class of medication that block the growth and spread of cancer by interfering with specific molecules that are critical for tumor progression, such as a particular tyrosine kinase. Different from traditional chemotherapy, which simply interferes with all rapidly dividing cells by interrupting essential cellular events such as DNA replication and microtubule assembly, targeted therapy focuses on molecular abnormalities specific to cancer. Such a mechanism allows targeted cancer therapy to be similarly or even more effective than chemotherapy and radiotherapy and less harmful to normal cells. Targeted therapies are composed of small-molecule drugs and monoclonal antibodies. The potential revolutionary success of targeted cancer therapy was first recognized in 1998, when a monoclonal antibody trastuzumab (Herceptin®) against receptor tyrosine kinase HER2 (ErbB2) was approved by the FDA for treating patients with HER2-positive metastatic breast cancer [74]. In 2001, imatinib targeting constitutively activated Bcr-Abl [85] was approved for the treatment of chronic myeloid leukemia (CML), which was the first rationally designed small-molecule inhibitor and is considered to start a new era in anticancer drug discovery. Thus far, over 30 targeted drugs have been approved in clinical use, alone or in combination with chemotherapy or other targeted therapies, for treating a broad range of human cancer types.

fibroblast growth factor receptor 1 (FGFR1), platelet-derived growth factor receptor alpha (PDGFRA) amplification have been defined in NSCLC. These genetic subtypes set the stage for different therapeutic options for NSCLC [12,13]. For example, *EGFR* activating mutations, mainly in-frame deletions in exon 19 and a missense mutation at codon 858 (L858R), are found in ~13% of NSCLC [13] cases and render patients responsive to EGFR inhibitors [14–16]. Currently, genotype screening for *EGFR* activating mutations is used to select patients to receive EGFR inhibitors as first-line treatment. Meanwhile, ~5% of NSCLC cancer patients harbor an *EML4* and *ALK* fusion gene, encoding a fusion protein with constitutive activation of ALK, and these patients do not benefit from EGFR inhibitors [17]. However, they exhibit a 57% response rate and 9-month progression-free survival after treatment with an ALK inhibitor [17,18]. *KRAS* mutations, which occur in ~24% of NSCLC cases and appear mutually exclusive with *EGFR* mutations or with *ALK* translocations, are a strong predictor of non-responsiveness to EGFR inhibitors [19]. As such, genetic testing for somatic mutations in lung cancer biopsies is becoming the routine procedure prior to drug treatment. The detection of *RAS* activating mutations leaves chemotherapy as the only option. Otherwise, testing for *EGFR* mutations or *ALK* translocations determines the possibility of treatment with EGFR or ALK inhibitors. As more targeted drugs are approved, it is expected that this roadmap will be modified to cover more subtypes, such as patients with *FGFR1* amplifications or *ROS1* translocations.

The roadmap for NSCLC drug treatment is a model for confronting the challenge of tumor heterogeneity, which is also present in other cancer types. A robust analysis of the genomic landscape in a discovery and validation set of 997 and 995 primary breast tumors has refined subgrouping of breast cancer [20]. The study revealed the important implications of acquired somatic copy-number aberrations (CNAs) or joint CNA and gene expression profiles in understanding therapeutic responses to targeted agents in breast cancer. According to the study, the integrated CNA expression landscape highlights a limited number of genomic regions that probably contain driver genes, including ZNF703, a luminal B-specific driver, and key subunits of the PP2A holoenzyme complex. Some low frequency (<1% patients) but potentially significant events, including insulin-like growth factor 1 receptor (*IGF1R*), *KRAS*, and *EGFR* amplifications and *CDKN2B*, *BRCA2*, *RB1*, *ATM*, *SMAD4*, *NCOR1*, and *UTX* homozygous deletions, have also been revealed. Likewise, based on a genome scale analysis, 276 human colon and rectal cancer samples were subgrouped into 16% of hypermutated and the rest non-hypermutated cancers [21]. The hypermutated malignancies are found to contain somatic mutations in mismatch-repair gene *MLH1* and polymerase ε (*POLE*). Meanwhile, 24 significantly mutated genes including *APC*, *TP53*, *SMAD4*, *PIK3CA*, *KRAS*, *ARID1A*, *SOX9*, and *FAM123B*, amplifications in *ERBB2* and *IGF2*, and chromosomal translocations such as *NAV2–TCF7L1* fusion were identified in the non-hypermutated samples [21]. These findings suggest new opportunities for the development of novel targeted agents to these defined cancer types.

The tumor microenvironment

Notably, the annotation of tumor heterogeneity and its implications in cancer therapy has extended to its interactions with microenvironments [6]. Microenvironment components, including blood and lymphatic vasculature, infiltrating normal cells, compositions of the extracellular matrix, and myriad factors such as lymphokines, cytokines, and chemokines, are not completely homogeneous. Tumor cells within a given tumor are expected to experience a range of microenvironmental cues, which would in turn translate into a range of phenotypic manifestations and thus variable responses to targeted therapy. A good example is the recent finding that secretion of hepatocyte growth factor (HGF) in the microenvironment confers *de novo* resistance to a BRAF inhibitor in melanoma cells [22]. The implications of the tumor microenvironment provide a glimpse into a more complete profile of heterogeneity between tumors [23].

Intratumor heterogeneity

Genetic diversity within tumors, as revealed especially by high-resolution genome-wide studies using next-generation sequencing (NGS), has important implications for targeted therapeutics [24,25]. Demonstrations of intratumor heterogeneity have challenged the notion of acquired resistance to targeted therapy, which, as implied by the term, has traditionally been believed to develop secondarily in response to treatment. It is increasingly realized that acquired resistance may sometimes, if not always, result from the outgrowth of resistant clones that were originally present in the primary cancer at low frequency and are enriched over time under the selective pressure imposed by targeted therapies [8]. This notion arises from studies into the molecular basis of acquired resistance to molecularly targeted therapies [26]. For example, the activating mutation T790M in the *EGFR* gene, which accounts for 50% of acquired resistance to the selective small molecule EGFR inhibitor gefitinib in NSCLC, was found to exist in a small