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Review

Roles of tumor heterogeneity in the development of drug resistance: A call for precision therapy

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ABSTRACT

The drug resistance limits the optimal efficacy of drugs during target therapies for lung cancer and requires the development of precision medicine to identify and develop new highly selective drugs and more precise tailoring of medicine to the target population. Lung cancer heterogeneity as a potential cause of drug resistance to targeted therapy may foster tumor evolution and adaptation and fade personalized-medicine strategies. The present review elucidates the influence of tumor heterogeneity on drug efficacy and resistance, and discusses potential strategies to combat heterogeneity for cancer treatment. There is an urgent need to discover and develop disease- and biology-specific biomarkers for monitoring the existence and occurrence of lung cancer heterogeneity, testing targeted drugs in clinical trials, and implementing precision medicine for patients. Better understanding of lung cancer heterogeneity will strengthen therapeutic strategies and apply precision medicine to cure the disease.

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1. Introduction

Precision medicine is proposed as a new strategy to identify and develop new highly selective drugs against specific targets for the disease and more precise tailoring of medicines to the target populations [1–3]. Precision medicine can be an important approach to create more novel and safer therapeutics for patients with gene fusions and mutation, methylation and acetylation, aberrations and variants, or protein over-expression [4]. Precision medicine requires an understanding of cancer genes, mutational processes, or heterogeneity between cancer cells during tumor evolution.

The tumor heterogeneity in diverse cancer types was evidenced by a meta-analysis of 2957 whole exomes and 126 whole genomes [5]. Inter-tumor heterogeneity with limited somatic alterations was noticed in histopathologic subtype tumors, while intra-tumor heterogeneity within individual tumor biopsies of the same tumor and temporally evolves during the disease course [6–8].

Patients with advanced solid tumors still have poor clinical outcome, due to the resistance to chemotherapeutics and targeted therapies [9].The tumor heterogeneity may exist between individuals, organs/tissues, locations, or cells [10,11] and contribute to

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low efficacy or failure of therapies through the development of drug resistance [12,13]. Acquired resistance could develop after an initial phase and be assessed by clinical phenotypes [14,15]. Resistance mechanisms were involved in secondary pathway mutations or bypass mechanisms within the tumor cells, such as EGFR(T790M)44 mutations or MET receptor amplification [16,17]. Understanding of lung cancer heterogeneity can help the development of predictive or prognostic biomarker strategies [18–21], to monitor the influence of tumor subclones in therapeutic efficacies and outcomes.

The present review briefly define various heterogeneities and potential associations with drug efficacy and resistance. We then overview new strategies to increase drug efficacy and minimalize the drug resistance and toxicity. We emphasize the importance to develop functional and precision biomarkers to monitor drug efficacy and resistance, and define opportunities and challenges of precision medicine for clinical practice.

2. Disease heterogeneity and drug efficacy

Tumor heterogeneity exists and develops between patients with or without genetic factors. A sequencing analysis of 3281 samples from 12 cancer types demonstrated that acute myeloid leukaemia was associated with the lowest mutational burden, while lung squamous cell carcinoma with the highest mutational burden [22,23]. Some somatic mutations e.g. methylmalonyl-CoA mutase −driver genes, caused interpatient tumor heterogeneity [24,25]. The high mutational burden of lung cancer samples was explained by the mutagenic effect of carcinogen exposures to e.g. cigarette smoke, and melanoma to ultraviolet radiation [26].

Lung cancer is a molecularly heterogeneous disease. The mutational landscape of lung adenocarcinoma is substantially different from that of squamous cell carcinoma or small cell lung cancer (SCLC), as shown in Table 1. About 10%-40% mutations in the tyrosine kinase domain of the epidermal growth factor receptor (EGFR) were noticed in lung adenocarcinomas [22,27], while rarely in squamous cell carcinoma and SCLC [22]. A number of TP53, KRAS, STK11, EGFR, and NF1 were mutated in adenocarcinomas, different from those classified by smoke status and gender. Mutations inTP53, KRAS, LKB1, NF1, and RBM10 were enriched in transversion-high tumors, while EGFR, RB1, and PIK3CA, and in-frame insertions in the receptor tyrosine kinases EGFR and ERBB2 in transversion-low tumors. Mutations in EGFR are associated with women, while RBM10 with men. Host genetic or non-genetic factors determine drug half-life, vascular permeability to drugs or acquired resistance to targeted drugs [28]. Cancers with low genetic mutational burden are associated with long lasting response to targeted therapy, whereas gene-unstable cancers with shorter duration of responses. The smoking-associated cancers with high levels of carcinogen-associated genetic mutations may be less to derive substantial long-term benefit from targeted therapy.

3. Micro-environment heterogeneity

The environment and/or microenvironment where the human and tumor cells live was recently identified as a factor to influence drug resistance and emphasized as the importance of the tumor cell extrinsic compartments [29,30]. The origin and influence of the micro-environment heterogeneity were involved in the recruitment of fibroblasts, migration of immune cells, matrix remodeling, and development of vascular networks [31–34]. Phenotypic and functional heterogeneity of cancer-associated fibroblasts could promote tumorigenesis, extracellular matrix production, and cytokine secretion, including stromal cell-derived factor 1,vascular endothelial growth factor, platelet-derived growth factor, and hepatocyte growth factor (HGF) [35]. Cancer-associated stromal secretion of HGF could activate the HGF receptor MET, mitogen-activated protein kinase (MAPK), and phosphatidylinositol-3-OH kinase (PI3K/AKT) signaling pathways, to have the immediate resistance to RAF inhibition [31]. The activation of MAPK and PI3 K/AKT-mTOR pathways regulates the formation of the eIF4F eukaryotic translation complex in BRAF(V600)-mutant tumors. The persistent formation of the eIF4F complex, binding to the 7-methylguanylate cap (m(7)G) at the 5' end of messenger RNA and modulating the translation of specific mRNAs, was associated with resistance to anti-BRAF, anti-MEK, and anti-BRAF plus anti-MEK drug combinations in BRAF(V600)-mutant melanoma, colon and thyroid cancer cells [33]. Microvessel density was reported to be a significant prognostic factor for poor outcome in NSCLC [36]. The expression of vascular endothelial growth factor-A was up-regulated with a worse prognosis in lung and renal cancers [37]. Tumor infiltrating lymphocytes may recognize neo-antigens presented on the surface of tumor cells as non-self, promoting enhanced T cell activation and immune cell tumor infiltration [38]. T cell activation was involved with stimulatory and inhibitory checkpoint signals to precisely tune responses to prevent excessive damage and autoimmunity. The usurping cytotoxic T cells can be activated in tumors through continuous engagement of inhibitory

Table 1
Heterogeneity of lung cancer.

Features		Adenocarcinoma	Squamous cell carcinoma	Small-cell lung cancer
Age-adjusted incidence (Incidence per 100,000 per year)		22.1	14.4	9.8
Napsin-A and TTF-1 immunostaining		Napsin-A (+) TTF-1 (+)	Napsin-A (−) TTF-1 (−)	Napsin-A (−) TTF-1 (+)
Genomic lateration	Mutations	TP53, KRAS, EGFR, NF1, BRAF, MET, RIT	TP53, CDKN2A, PIK3CA, NFE2L2, KEAP1, CUL3, PTEN, NF1, NOTCH1,2, and 3, DDR2, EGFR	TP53, RB1, EP300, CREBBP, PTEN, SLIT2
	Fusions	ALK, ROS1, RET,NTRK1,RASSF1A,FZR2	FGFRs	
	Somatic copy number alteration	Gains: NKX2-1, TERT, EGFR, MET, KRAS,ERBB2, MDM2 Losses: LRP1B, PTPRD, and CDKN2A	Gains: Chr 3q 26 (SOX2, PIK3CA, TP63 etc) Losses: CDKN2A, PTEN	Gains: MYC, MYCN, MYCL1, SOX2, FGFR1, KIT Losses: Chr 3p (FHIT, FUS1, RASSF1A)
	Pathway alterations	RTK/RAS/RAF mTOR JAK-STAT DNA repair Cell cycle regulation Epigenetic deregulation	Squamous diff erentiation Oxidative stress response PIK3CA DNA repair Cell cycle regulation Epigenetic deregulation	Hedgehog, DNA repair,axonal guidance and neuroendocrine diff erentiation, Cell cycle regulation, epigenetic deregulation,

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