Cancer Letters 387 (2017) 69–76

Contents lists available at ScienceDirect

Cancer Letters

journal homepage: www.elsevier.com/locate/canlet

Mini-review

Overcoming treatment resistance in cancer: Current understanding and tactics

Guang Wu [a], George Wilson [a], Jacob George [a], Christopher Liddle [a], Lionel Hebbard [a,b,*], Liang Qiao [a,**]

[a] Storr Liver Centre, The Westmead Institute for Medical Research, The University of Sydney, Westmead, NSW 2145, Australia
[b] Department of Molecular and Cell Biology, James Cook University, Townsville, QLD, Australia

ARTICLE INFO

Keywords:
Treatment resistance
Cancer stem cells
Cancer progression
Mutation
EMT
EMT transition

ABSTRACT

Chemotherapy is the standard treatment for many, if not all, metastatic cancers. While chemotherapy is often capable of inducing cell death in tumors leading to shrinkage of the tumor bulk, many patients suffer from recurrence and ultimately death due to resistance. During the last decade, treatment resistance has attracted great attention followed by some seminal discoveries, including sequential mutations, cancer stem cells, and bidirectional inter-conversion of stem and non-stem cancer cell populations. Nevertheless, the successful treatment of cancer will require a considerable refinement of our knowledge concerning treatment resistance. In doing so, we expect that a more informed and refined approach to treat cancer will be developed and this may improve prognosis of cancer patients. In this review, we will discuss the current knowledge concerning the failure of cancer treatments and the potential approaches to overcome therapeutic resistance.

Introduction

Due to advances in oncology research our understanding of cancer has changed dramatically over last decade. The tumor itself is not only recognized as an aggregation of excessive, uncontrolled abnormal cells but is also characterized by dynamic changes in the genome leading to the initiation and progression of cancer [1]. In addition, the long-held hypothesis, in which every single cell has the same capacity in terms of invading and colonizing other parts of the body, has been challenged by heterogeneous cancer stem cells (CSCs) models [2]. Moreover, a new model of "plastic cancer stem cells", in which non-CSCs can be trans-differentiated into CSCs in response to certain stimuli, has further broadened our view of cancer [3]. These discoveries have provoked a rapid development of treatment options for cancer therapy, including surgery, radiation, cytotoxic chemotherapy and more selective treatments derived from the increased understanding of biological features of distinct tumor subtypes [4].

Chemotherapy has long been the approach of choice for the treatment of tumors that are not suitable for radical resection because of advanced stage. However, these tumors possess the uncanny ability to resist the effects of cancer chemotherapeutic agents, and after an initial robust response, the tumors reappear. In this light near 90% of the drug failures in metastatic cancers can be attributed to resistance [5]. Resistance to chemotherapeutics can be divided into two categories: intrinsic and acquired [6]. The former indicates the presence of pre-existing mediators leading to inefficacy towards a given treatment, while the later represents the emerging resistance against an initially effective therapeutic regime. In as much, numerous studies focusing on treatment resistance are being published. Therefore, we will now review the current understanding of cancer treatment failure and consider approaches that can better treat these malignancies.

Abbreviations: ABCB1, ATP-binding cassette, Sub-family B, Member 1; ABCG2, ATP-binding cassette, Sub-family G, Member 2; AKT, V-Akt murine thymoma viral oncogene; APC, adenomatous polyposis coli; AQ4N, di-N-oxide aliphatic amino anthracenedione; BRAF, b-Raf proto-oncogene; BRCA, breast cancer gene; CDK2N, cyclin-dependent kinase 2; CSCs, cancer stem cells; EGFR, epidermal growth factor receptor; EMT, epithelial to mesenchymal transition; ER, estrogen receptors; FBXW7, f-box and WD repeat domain containing 7; HCC, hepatocellular carcinoma; HDAC, histone deacetylase; HIF, hypoxia inducible factor; KRAS, the human homolog of the Kirsten rat sarcoma-2 virus oncogene; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase; MMPs, matrix metalloproteinase; NF, nuclear factor; NRAS, neuroblastome RAS viral oncogene:; NSCLC, non-small cell lung carcinoma; PIK3CA, phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit alpha; PTEN, phosphatase and tensin homolog; siRNA, small interfering RNA; SAHA, suberoylanilide hydroxamic acid; SMAD4, SMAD family member 4; SP, side population; TERT, telomerase reverse transcriptase; TGF-β1, transforming growth factor, beta 1; TIMP-2, tissue inhibitor of matrix metalloproteinase-2; TMZ, Temozolomide; TP53, tumor protein 53; ZEB1, zinc finger E-box binding homebox 1.

* Corresponding author. Tel.: +617 4781 5684.
E-mail address: lionel.hebbard@jcu.edu.au (L. Hebbard).
** Corresponding author. Tel.: +612 86273534; fax: +612 86273099.
E-mail address: liang.qiao@sydney.edu.au (L. Qiao).

http://dx.doi.org/10.1016/j.canlet.2016.04.018
0304-3835/

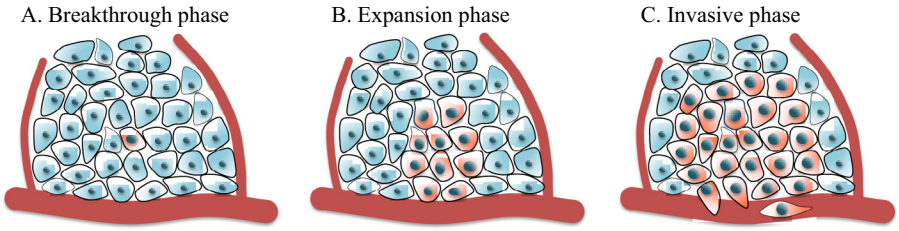

Fig. 1. Sequential mutations and treatment resistance. A. At breakthrough phase, one cell starts proliferating abnormally upon acquiring the mutation. B. Cells with the first mutation attain the second one in the expansion phase leading to fast expansion of malignant cells. C. In the invasive phase, cells develop another mutation, enabling them to metastasize into surrounding tissues.

Sequential mutations and treatment resistance

One model to explain the emergence of cancer drug resistance is based on the accumulation of mutations throughout the progression of a tumor. The evolution of a tumor can be artificially divided into three phases: breakthrough phase, expansion phase and invasive phase [1] [Fig. 1]. In the breakthrough phase, a tumor cell begins to grow abnormally due to the acquisition of specific gene mutations. These mutated cells then attain a second mutation in the expansion phase, where they can then thrive in an ill-disposed microenvironment, such as low oxygen tension, nutrient-deprived or over-crowding. Following the invasive phase further mutations are acquired to promote tumor cell invasion and metastasis, the hallmarks of end stage malignancy.

Evidence of the accumulated mutation model in human tumors has been published and some of these we will now discuss. The dominant mutation for the breakthrough phase of pancreatic ductal adenocarcinoma is KRAS (the human homolog of the Kirsten rat sarcoma-2 virus oncogene) followed by CDKN2A (cyclin-dependent kinase 2) mutations, occurring at a rate greater than 50%, which promotes the expansion of transformed cells. For the invasive phase, SMAD4 (SMAD family member 4) and TP53 (tumor protein 53) mutations have been identified [7,8]. Due to the distinct driver mutations at different stages of pancreatic cancer, it is not surprising that current therapeutic strategies, using a non-specific approach to patient recruitment, have kept the median survival of pancreatic cancer patients at 6 months and a 5-year survival rate of below 5% [9]. One way to improve therapeutic efficacy is obviously to develop personalized treatment based on disease genotype. For instance, gemcitabine-based chemotherapy is the first-line treatment option for advanced pancreatic adenocarcinoma. However, patients with KRAS mutations (71 out of 136 patients) showed worse response than those with wild-type KRAS [10]. In order to overcome gemcitabine resistance in advanced pancreatic carcinoma, Maria et al [11] generated personalized xenograft mice model using gemcitabine-resistant human pancreatic tumors and demonstrated that additional administration of mitomycin C (MMC), a DNA damaging agent resulting in long-lasting (>36 months) tumor response. Mechanistic studies revealed that mutation of PALB2 (Parter and Localizer of BRCA2) is a key determinant of response to MMC. In addition, a recent sequencing study of pancreatic cancer has shown structural variation (the variation in structure of the tumor cell chromosome) as an important mutational mechanism in pancreatic carcinogenesis. This finding led the authors to further subdivide pancreatic cancer into four groups based on the frequency and distribution of structural rearrangements: (i) stable, (ii) locally rearranged, (iii) scattered, and (iv) unstable subtype. Clinical and animal studies have revealed that unstable genome and a high BRCA mutational signature burden were associated with poorer response to platinum-based therapy [8]. Although these studies have potential implications for selecting the appropriate therapeutic options for pancreatic cancer, the putative biomarkers defined by these data need further testing in a large clinical trials,

In colon cancer, APC (adenomatous polyposis coli) mutations initiate the neoplastic process, and the expansion phase is driven by KRAS mutations, leading to the progression from colorectal adenoma to carcinoma. Further mutations of TP53, SMAD4, PIK3CA (phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit alpha) or FBXW7 (F-box and WD repeat domain containing 7) can promote invasion into the surrounding tissues. Independent studies have also shown the importance of KRAS mutations as they were detected in over one-third of the colorectal cancer (CRC) tissues [12]. Cetuximab, a monoclonal antibody that binds the extracellular domain of epidermal growth factor receptor (EGFR), has been shown to be effective against a subset of KRAS wild-type metastatic CRC cases. However, a majority of patients develop resistance after an initial response and further analysis of the resistant tumors confirmed the acquisition of secondary KRAS mutations in 60% of them, indicating that KRAS mutations are frequent drivers of acquired resistance to EGFR inhibition [13].

Melanomas often arise from distinctive precursor lesions such as melanocytic nevi, intermediate lesions, or melanoma *in situ*. By DNA sequencing and functional experiments, it has been found that precursor lesions are initiated by mutations of genes capable of activating the mitogen-activated protein kinase (MAPK) pathway [14]. However, only benign lesions harbor BRAF (B-Raf proto-oncogene) V600E mutations and intermediate lesions are enriched for mutations of NRAS (neuroblastoma RAS viral oncogene) and additional driver genes, such as BRAF V600K or BRAF K601E. TERT (telomerase reverse transcriptase) promoter mutations were found in 77% of the areas of intermediate lesions and melanomas *in situ*. In contrast, biallelic inactivation of CDKN2A is exclusively associated with invasive melanomas, while PTEN (phosphatase and tensin homolog) and TP53 mutations were found mainly in advanced primary melanomas. These studies might help explain why chemotherapy may work at the early phase of treatment but not as effective as a targeted therapy in melanoma [15]. Dacarbazine, the most effective systemic chemotherapeutic agent approved by FDA for advanced melanoma, only has a response rate of 10–20% with complete remission in only 5% of patients [16]. Increased expression of BCL-2 in tumor tissues and associated resistance to apoptosis is one of the mechanisms responsible for treatment resistance in patients with KRAS mutations [17,18]. Studies from multiple centers have shown that combination of oblimersen (a BCL-2 antisense oligonucleotide) with dacarbazine significantly improved clinical outcomes of patients with advanced melanoma [19]. This funding prompted further clinical trials on whether the addition of oblimersen should be suggested as the first line treatment for patients with melanoma harboring NRAS mutation. As BRAF mutation exist in the vast majority of melanoma cases, FDA has approved two BRAF inhibitors vemurafenib and dabrafenib for the treatment of unresectable or metastatic melanoma [20]. However, resistance to these agents