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Cancer stem cells in drug resistant lung cancer: Targeting cell surface markers and signaling pathways☆

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ABSTRACT

Lung cancer is the leading cause of cancer mortality worldwide. Despite advances in anti-cancer therapies such as chemotherapy, radiotherapy and targeted therapies, five-year survival rates remain poor (<15%). Inherent and acquired resistance has been identified as a key factor in reducing the efficacy of current cytotoxic therapies in the management of non-small cell lung cancer (NSCLC). There is growing evidence suggesting that cancer stem cells (CSCs) play a critical role in tumor progression, metastasis and drug resistance. Similar to normal tissue stem cells, CSCs exhibit significant phenotypic and functional heterogeneity. While CSCs have been reported in a wide spectrum of human tumors, the biology of CSCs in NSCLC remain elusive. Current anti-cancer therapies fail to eradicate CSC clones and instead, favor the expansion of the CSC pool and select for resistant CSC clones thereby resulting in treatment resistance and subsequent relapse in these patients. The identification of CSC-specific marker subsets and the targeted therapeutic destruction of CSCs remains a significant challenge. Strategies aimed at efficient targeting of CSCs are becoming increasingly important for monitoring the progress of cancer therapy and for evaluating new therapeutic approaches. This review focuses on the current knowledge of cancer stem cell markers in treatment-resistant lung cancer cells and the signaling cascades activated by these cells to maintain their stem-like properties. Recent progress in CSC-targeted drug development and the current status of novel agents in clinical trials are also reviewed.

Contents

Abbreviations: ABC, ATP-binding cassette transporters; ALDH, aldehyde dehydrogenase; CD, cluster of differentiation; CLL, chronic lymphocytic leukemia; CSC, cancer stem cell; CSC-DC, cancer stem cell lysate-pulsed dendritic cell; DAPT, N-[N-(3,5-difluorophenacetyl)-1-alanyl]-S-phenylglycine t-butyl ester; Dv1, disheveled inhibitor; EMT, epithelial to mesenchymal transition; FDA, food and drug administration (USA); GLDC, glycine decarboxylase; Gli1, GLI family zinc finger 1; GSI, gamma secretase inhibitor; HIP, Sonic hedgehog (Shh)-interacting protein; JNK, c-Jun N-terminal kinase; miRNA, microRNA; NFκB, nuclear factor-kappa beta; NSCLC, non-small cell lung cancer; PI3K, phosphatidylinositol-3-kinase; SCID, severe combined immunodeficiency; SCLC, small cell lung cancer; Shh, Sonic hedgehog; SMO, G-coupled receptor smoothened.

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1. Introduction

Cancer is a leading cause of death worldwide. It accounted for 8.2 million deaths in 2012, of which 1.59 million were due to lung cancer (Ferlay et al., 2015). Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases and is divided into a number of histological subtypes; adenocarcinoma, squamous cell carcinoma and large cell carcinoma. At diagnosis, approximately 70% of patients present with locally-advanced or metastatic disease and require systemic treatment (Horner et al., 2009). Despite advances in chemotherapy and radiotherapy, in addition to personalized treatments with therapies targeting EGFR and EML4-ALK in specific patient subgroups, five years survival rates remain poor (<15%).

Platinum-based doublet chemotherapy is the gold standard therapy for NSCLC patients in the first line setting, where cisplatin or carboplatin is used in combination with gemcitabine, vinorelbine, pemetrexed or taxanes (docetaxel or paclitaxel). Such combination regimens containing platinum agents have demonstrated overall response rates of 25–35% median progression-free survival of 4–6 months and overall survival of approximately 8–10 months (Azzoli et al., 2009; Reck et al., 2014). While many lung cancer patients initially respond to therapy, 20–40% of patients tend to relapse within six months (Giaccone et al., 1998). It is now well established that this may be due to the emergence of a resistant tumor phenotype during treatment with chemotherapy (Gower, Wang, & Giaccone, 2014). While conventional cytotoxic therapies eliminate the bulk of tumor cells within the lung tumor cell population, a subset of residual cancer cells continue to proliferate and survive. These have since been classified as cancer stem cells (CSCs), a distinct population of tumor cells that have the ability to self-renew, differentiate and promote tumor growth (Reya, Morrison, Clarke, & Weissman, 2001).

During the past decade, CSCs have been increasingly identified in many malignancies. Although the exact origin of these cells remains controversial, tumor heterogeneity and the presence of small populations of cells with characteristic stem-like properties have been established in most tumor types. CSCs display many features of embryonic or tissue stem cells, and typically demonstrate persistent activation of one or more highly conserved signal transduction pathways involved in development and tissue homeostasis, including the Notch, Hedgehog, and Wnt pathways (Takebe et al., 2015). Dysregulation of these key signaling pathways plays an important role in enabling CSCs to retain their stem-like properties and are crucial for the tumorigenicity of these cells. Such pathways may constitute important therapeutic targets for the blockade of CSC self-renewal, proliferation and tumor progression (Merchant et al., 2010). CSCs have slower growth rates than tumor cells and are resistant to chemotherapy and/or radiotherapy. Therefore, new treatment strategies targeting these signaling pathways are warranted to control stem-cell replication, survival and differentiation. This review will focus on the various cancer stem cell markers and signaling pathways utilized by CSCs in the context of drug resistant lung cancer. It will also provide an update on the latest advances in the clinical development of such approaches and discuss potential strategies for CSC-directed therapy to overcome resistance to cancer treatment.

2. Chemoresistance in lung cancer

The current standard of care for localized NSCLC (stage II and III disease) is surgery, followed by adjuvant cisplatin-based chemotherapy. In a pooled analysis of the five largest trials to date using data from 4585 patients treated with cisplatin-based chemotherapy, the Lung Adjuvant Cisplatin Evaluation Program (LACE) demonstrated a five-year survival benefit of 5.4% using adjuvant chemotherapy, with an overall hazard ratio (HR) of 0.89 (Pignon et al., 2008). Platinum-based cytotoxic agents, such as carboplatin, oxaliplatin, and in particular cisplatin, are commonly used in the treatment of lung cancer. Whether these are used as part of neoadjuvant, adjuvant or palliative therapy, disease localization and survival are notably increased when platinum-based agents are used in the clinical setting (Cosaert & Quoix, 2002). In patients with advanced NSCLC, platinum-based drugs have been shown to increase the 1-year survival rate by 5% when compared to non-platinum agents alone, but show equal efficiency with third generation adjuvant therapies (D'Addario et al., 2005). While cisplatin was first synthesized in 1844 and its chemical structure was first elucidated several years later in 1893, significant interest in this platinum compound came about following observations by Rosenberg, Van Camp, and Krigas (1965) at Michigan State University that electrolysis products of platinum electrodes were capable of inhibiting cell division in *Escherichia coli*. Such findings initiated an interest in the possible use of these products in cancer chemotherapy and the subsequent identification of the active agent responsible for this activity, cis-dichlorodiammineplatinum(II) (cisplatin). By the end of the 1970s, cisplatin had earned its place as the key agent in the systemic treatment of germ cell cancers and was FDA-approved for use in cancer treatment in 1978 (Kelland, 2007; Frezza et al., 2010).

The anti-cancer activity of cisplatin is based on the formation of cisplatin-DNA adducts in the nuclear DNA (Boulikas & Vougiouka, 2003) (Fig. 1). To date, several of these platination products have been identified, where the guanine–guanine intrastrand crosslink, cis-Pt(NH3)2d(pGpG) [Pt-(GG)], represents >70% of total DNA platination (Barr et al., 2013). The presence of such lesions within cellular nuclear DNA results in aberrant replication and transcription and has been reported to induce multiple signaling transduction pathways and proteins, such as p53, Bcl-2, cyclins, caspases, CDKs, PKC, MAPK and PI3K/Akt to trigger cell cycle arrest and apoptosis (Ryan, Phillips, & Vousden, 2001; Wu, Mehew, Heckman, Arcinas, & Boxer, 2001; Johnstone, Ruefli, & Lowe, 2002; Vivanco & Sawyers, 2002; Chipuk et al., 2004; Wang, Reed, & Li, 2004). The outcome of cisplatin therapy in NSCLC has however reached a plateau, with the development of resistance being a major clinical challenge in the use of this drug. Resistance of tumor cells to such cytotoxic therapies can manifest as either innate or acquired, and critically limits treatment outcomes for patients thereby presenting a significant problem in the clinical setting (Chang, 2011). Several mechanisms have now been identified that are responsible, at least in part, for the resistant phenotype found in tumor cells, particularly in relation to the platinum agent, cisplatin. These include reduced

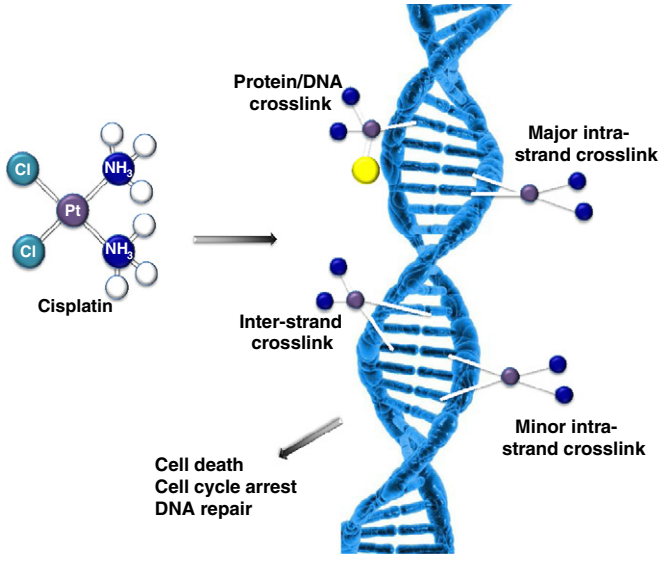

Fig. 1. Cisplatin formation of DNA adducts. Once inside the cell, cisplatin forms DNA adducts. These can manifest as major intra-strand crosslinks (1,2-), minor intra-strand crosslinks (1,3-), inter-strand crosslinks or DNA/protein crosslinks, and induce a range of cellular responses, typically including apoptosis, induction of DNA repair and cell cycle arrest.