Molecular Biology
ISSN: 2168-9547
Okon, Mol Biol 2015, 4:4
DOI: 10.4172/2168-9547.1000140
Commentary Open Access

Cancer Drug Resistance: The Why, The How and The What-Next?

Imoh S. Okon*
Center for Molecular and Translational Medicine, Georgia State University, Atlanta, USA

Introduction

Astronomic advances in cancer therapy has been achieved in recent years. Specifically, the last 10-20 years has witnessed the advent of target-specific anti-cancer agents that have provided relative but significant benefits. Traditional chemo and radio–therapy approaches, while still in use and necessary in certain cases (instances) lack target specificity which means that off-target, bystander effects to non-cancer cells could be detrimental, and trigger gene mutations that fuel the initiation of "new" malignant cells. Beyond potential alterations to non-cancer cells, the import and wider implications of non-targeted cancer therapies are unknown, and may likely impact several cellular signaling events. Therefore, the emergence of tyrosine kinase inhibitors (TKIs) that target specific aberrantly expressed or activated genes has provided an alternative approach that minimizes off-target effects. Classic TKIs such as, Iressa (gefitinib) and Tarceva (erlotinib) target the EGF receptor (EGFR) via reversible competition against phosphate groups for tyrosine binding sites in the intracellular domain of the receptor [1]. These phosphate groups are usually from ATP/ADP transitions, thus providing a direct link to cellular energy status within cells. While EGFR activation through ligand-binding to EGF can occur in a paracrine-dependent manner, the receptor can also undergo activation via an autocrine mechanism (autophosphorylation) [2]. Ligand binding instigates conformational changes within the receptor that exposes intracellular tyrosine docking sites, enabling binding of phosphate groups, and subsequent receptor dimerization and activation. Classic EGFR signaling cascades involve the activation of the receptor and recruitment of adaptor molecules (eg. Src, c-cbl, shc, Grb2) that possess unique sequence motifs/domains [1,2]. In turn, these sequence of events modulate specific downstream signaling pathways, such as proliferation, apoptosis, migration, and related cellular processes critical to tumor growth and survival [1-4]. While gefitinib and erlotinib have been mainly used against pancreatic cancer, non-small cell lung cancer (NSCLC) and other cancer types, the humanized monoclonal antibody, trastuzumab (Herceptin) blocks *HER2* (*Erbb2*) breast cancer gene [5-7]. As would be expected, HER2-positive breast cancer patients derive the most benefits from trastuzumab. Obviously, cancer treatments and specific targeting of defective cancer-promoting genes is not a straight-forward process. Several factors, such as mutations within the target genes result in differential response to treatments [5,8]. Importantly, specific EGFR mutations have been shown to determine or influence the degree response to gefitinib [5,8].

The Why and the How?

While relative benefits have been provided by various TKIs, the reversible nature of these agents result in limited benefits, thereby requiring the maintenance of certain therapeutic levels in circulation to achieve desired effects. Furthermore, acquired resistance to gefitinib/erlotinib present additional problems with reversible TKIs [6]. These drawbacks resulted in the push for new strategies, and eventual development of irreversible inhibitors, which theoretically should provide a better approach at shutting down activation and signaling events from aberrant receptors. For example, Afatinib (BIBW 2992), an irreversible EGFR-TKI has been used against advance NSCLC with relative benefits [9]. However, the overall benefit and roles of irreversible TKIs remain to be fully deciphered [9]. While these advances in novel anti-cancer agents have provided relative benefits, a major problem unique to all cancer therapies is drug resistance [10]. While the "window" of response to different agents may vary, the endpoint or eventual outcome of many treatments is decreased or complete lack of response of cancer cells to previously sensitive therapy. Drug resistance is therefore a consistent occurrence irrespective of the anti-cancer agents in use. Furthermore, the pattern of drug resistance transition suggest that cancer cells undergo adaptations in response to chronic drug treatments that enable the circumvention of deleterious effects. The nature of these alterations, and factors that regulate the transition is critical to gaining novel insights in order to better understand drug resistance, and design more effective therapies. Beyond solid tumors, resistance to TKIs also occur in leukemia patients, such as chronic myelogenous leukemia (CML) and acute lymphoblastic leukemia (ALL) [11,12]. The Bcr-Abl TKI is a first-line therapy commonly used in CML patients, and BCR-ABL$^+$ ALL [11,12]. However, resistances rapidly sets in, and the underlying mechanisms, like previously observed with solid tumors remains largely unknown. Interestingly, resistance to BCR-ABL$^+$ has been associated with the expression of specific genes which in turn instigate a switch in survival signaling pathways [12]. This finding is in agreement with the notion that genetic aberrations are the "root" cause of drug resistance, albeit facilitated or escalated by intrinsic or extrinsic factors.

Following the onset of cancer initiation via genetic, environmental or other factors, various processes are critical to the growth and survival of cancer cells. Such factors include dysregulated cell cycle, uncontrolled proliferation, attenuated apoptosis, metabolic alterations, enhanced angiogenesis and motility. It is therefore conceivable that drug resistance transition may involve perturbations to one or more of these processes. To achieve this, the genetic "gate-keepers" that regulate the processes are usually compromised. However, the wide divergence in cancer-drivers, and mechanisms of action of prescribed therapies most likely determine what adaptations cancer cells employ during drug resistance transition. For chemo or radio –therapy agents, increased reactive oxygen species (ROS) may serve as the prominent pathway or fuel that instigates dysregulation of cellular processes and functions. Conversely, agents such as TKIs or monoclonal antibodies may instigate drug resistance via other routes, such as alterations to metabolism or immune response, respectively. The complexity, dynamic nature and resilient survival adaptations inherent within cancer cells contribute to the utilization of multiple mechanisms in order to achieve resistance. For example, in our study, we observed that in addition to defective cell cycle and increased ROS, chronic gefitinib treatment resulted in perturbations to mitochondrial morphology and functions [5].

Conclusion: The What-Next?

While significant progress has been recorded in the treatment of

***Corresponding author:** Imoh S. Okon, Center for Molecular and Translational Medicine, Georgia State University, Atlanta, USA, E-mail: iokon@gsu.edu

Received October 02, 2015; **Accepted** October 15, 2015; **Published** October 22, 2015

Citation: Okon IS (2015) Cancer Drug Resistance: The Why, The How and The What-Next? Mol Biol 4: 140. doi:10.4172/2168-9547.1000140

many cancer types, there remains the major hurdle of overcoming resistance to previously responsive drugs. Transition towards drug resistance appear to be progressive events that occur over time, a critical "window" that allow adaptations to occur within a small sub-population of cancer cells in response to a particular drug. Acquisition of unique properties and phenotypes by resistant cancer cells support survival, expansion and the thriving of such "rogue" cells which eventually result in decreased or complete lack of response to therapy. While identification of new drug targets and delivery approaches is critical, a fundamental understanding of the processes and alterations that drive drug resistance transition is of greater significance. Therefore, the identification of key players associated with the transition process is an important starting point. Technological advances in basic and translational cancer research will facilitate robust and accurate characterization of drug resistance markers (DRMs). In addition to identification of DRMs, our group is working to determine and define the "hallmarks" of drug resistant cancer cells. To achieve this, we are investigating and systemically sorting out differences between sensitive and resistant cancer cells in a drug-dependent manner. This approach will guide optimum drug selections for combinatorial strategies. Furthermore, such information will drive the design of new cancer drugs or influence modifications to existing agents in order to prolong the window of drug efficacy and response.

References

1. Roskoski, R. (2004) The ErbB/HER receptor protein-tyrosine kinases and cancer. *BBRC* 319, 1–11.
2. Yarden, Y. (2001) The EGFR family and its ligands in human cancer: signaling mechanisms and therapeutic opportunities. *Eur J Cancer* 37, S3-8.
3. Gullick, W. J. (1991) Prevalence of aberrant expression of the epidermal growth factor receptor in human cancers. *Br Med. Bull.* 47, 87–98.
4. Okon, I.S., Coughlan, K.A., and Zou, M-H. (2013) Liver Kinase B1 Expression Promotes Phosphatase Activity and Abrogation of Receptor Tyrosine Kinase Phosphorylation in Human Cancer Cells. *J Biol Chem* 289: 1639-1648.
5. Okon, I.S., Coughlan, K.A., Zhang, M., Wang, Q., and Zou, M-H. (2014) Gefitinib-mediated Reactive Oxygen Species (ROS) Instigates Mitochondrial Dysfunction and Drug Resistance in Lung Cancer Cells. *J Biol Chem* 290 : 9101-9110.
6. Chen Y.M. (2013) Update of epidermal growth factor receptor-tyrosine kinase inhibitors in non-small-cell lung cancer. *J Chin Med Assoc* 76: 249-257.
7. Shabani, M., and Hojjat-Farsangi, M. (2015) Targeting Receptor Tyrosine Kinases using Monoclonal Antibodies: The Most Specific Tools for Targeted-Based Cancer Therapy. *Curr Drug Targets* [Epub ahead of print].
8. Lopes, G.L., Vattimo, E.F., and Castro, J.G. (2015) Identifying activating mutations in the EGFR gene: prognostic and therapeutic implications in non-small cell lung cancer. *J Bras Pneumol* 41(4): 365-75.
9. Maione, P., Rossi, A., Bareschino. M., Sacco, P.C., Schettino, C., et al. (2014) Irreversible EGFR Inhibitors in the Treatment of Advanced NSCLC. Curr Phar Des. 20: 3894-3900.
10. Okon, I.S. and Zou, M-H. (2015) Mitochondrial ROS and cancer drug resistance: Implications for therapy. *Pharmacol Res*. 100, 170-74.
11. *An, X., Tiwari, A.K., Sun, Y., Ding, P.R., Ashby, C.R. Jr., and Chen, Z.S. (2010) BCR-ABL tyrosine kinase inhibitors in the treatment of Philadelphia chromosome positive chronic myeloid leukemia*: a review. *Leuk Res*. 34: 1255-1268.
12. Mallampati, S., Leng, X., Ma, H., Zeng, J., Li, J., et al. (2015) Tyrosine kinase inhibitors induce mesenchymal stem cell-mediated resistance in BCR-ABL+ acute lymphoblastic leukemia. Blood 125 : 2968-2973.