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Identification of the specific epigenetic alterations associated with chemo-resistance via reprogramming of cancer cells

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ABSTRACT

Background: Chemo-resistance is the main obstacle in cancer therapy, limiting the effectiveness of drug treatment. Epigenetics-mediated changes are suggested as a critical factor paying the chemo-resistance phenotype. Since epigenetic modulations are a reversible phenomenon, reversion of epigenetic changes represents a promising therapeutic approach for cancer. However, heterogeneity in epigenetic marks in tumor cells makes it difficult to identify the specific epigenetic aberrations contributing to chemo-resistance. Our hypothesis aimed to explore this issue to add therapeutic options for cancer.

Presentation of the hypothesis: Epigenetic alterations, the main mediator of cellular reprogramming, occur rapidly upon exposure to chemotherapy. Recent studies have demonstrated that reprogramming resets/erases the epigenetic marks established during differentiation to specific somatic cell types. To overcome the heterogeneous nature of cancer cells, we will attempt to make homogenous cancer cell colonies by reprogramming. Comparison of the drug-resistant cancer cells obtained from these colonies to parent cancer cells and reprogrammed cancer cells is an effective way to determine the precise epigenetic alterations underlying specific chemo-resistance.

Testing the hypothesis: Cellular reprogramming of cancer cells led to generation of homogenous colonies. Following lineage specification and long term drug treatment, the obtained drug resistance cells will be compared with parent cancer cells for whole genome epigenetic signature.

Implications of the hypothesis: A key implication of this hypothesis is that determination of the usefulness of cellular reprogramming of cancer cells enabling the identification of specific epigenetic modulation associated with particular drug resistance will enable exploration of new research avenues for cancer treatment.

Background

Cancer, which is a highly deadly disease worldwide, is commonly treated by chemo-, radio- and hormonal-therapy, and surgical modulation [1]. Chemotherapy is an effective treatment option for several cancers depending on the patient's age, health, cancer type and stage [2]. However, resistance (either intrinsic or acquired) of cancer cells to various therapeutic agents and modalities is the most serious issue in clinical oncology. Indeed, this limits the effectiveness of anti-cancer drug treatment, thereby contributing to uncontrolled tumor progression and minimizing chances of cancer abolishment [3–6]. The mechanism of drug resistance involves various phenomena including genomic instability, decreased drug activation or increased drug degradation by enzymes, altered membrane permeability/transporters of drug and inability to reach the target sites, mutation and altered expression of target proteins there by affecting drug target interactions, altered drug metabolism, activation of downstream or parallel signal transduction pathways [7–11].

With advances in molecular biology, recent studies have suggested the potential role of various epigenetic or non-genetic factors in driving drug resistance in cancer [12–14]. Consequently, multiple studies have shown that, upon drug treatment, cancer

Abbreviations: ABCB1, ATP-Binding Cassette, Sub-Family B; MDR, Multi Drug Resistance; DAPK, Death Associated Protein Kinase; APAF-1, Apoptotic Peptidase Activating Factor 1; MLH1, MutL Homolog 1; MGMT, O-6-Methylguanine-DNA Methyltransferase; KDM5A, Lysine (K)-Specific Demethylase 5A; MEK, Mitogen-Activated Protein Kinase Kinase 1; IGF-1R, Insulin Growth Factor Receptor-1; DNA, Deoxyribonucleic Acid; DNMT1, DNA (Cytosine-5-)-Methyltransferase 1; HDAC1, Histone Deacetylase 1; ALP, Alkaline Phosphatase; RT-qPCR, Reverse Transcription-quantitative Polymerase Chain Reaction; RNA, Ribose Nucleic Acid; OGs, Oncogenes; pOGs, proto-oncogenes; TSGs, Tumor suppressor genes.

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cells adjust the architecture of their own DNA via major epigenetic mechanisms that cause modifications in the expression of genes responsible for chemo-resistance, including drug transporters (ABCB1, MDR) [15–17], pro-apoptotic genes (DAPK, APAF-1) [18,19], DNA-repair proteins (MLH1 [20], MGMT [21]) or histone modifiers (KDM5A, [22]), as well as MEK and IGF-1R signal transduction pathway activation via reduction of H3K4me and H3K14ac histone marks [5,19]. Since, chemo-resistance involves alteration of the expression of an enormous number of genes, and epigenetic changes occur more rapidly upon chemotherapy exposure, epigenetic-signatures such as histone posttranslational modifications, DNA hypermethylation, and subsequent gene silencing are of increasing importance and a more accurate mechanism accounting for the acquisition of drug-resistance by affecting the expression of many hundreds of genes [23–25]. This has led to new conjecture of reversion of drug resistance by reactivation of drug sensitivity genes using epigenetic drugs to re-sensitize tumors to chemotherapy. DNMT1 and HDAC1 have shown considerable promise for this application, and clinical trials of such epigenetic therapies are now being evaluated [26,27]. However, exact characterization of epigenetic regulation over chemo-resistance is still a major and unresolved puzzle particularly in acquired resistance during long term drug exposure. This requires further studies to increase our understanding of their potential mechanisms of action.

Identification of specific epigenetic modulations that contributes to cancer progression by selective chemo-resistance is challenging when based only on comparison of drug-resistant and drug-sensitive cancer cells because of inherent heterogeneity in the epigenetic makeup of tumor cell populations as well as intrinsic resistance [28]. To obtain authentic chemo-resistance-specific epigenetic modifications, comparisons must be made within homogenous cells or in the same cell with and without epigenetic modification. Cellular reprogramming is a phenomenon that changes the cell from its state to a pluripotent state without altering the genetic profiles via reset or erasing the pre-existing epigenetic signature [29–31]. Comparison of drug-sensitive homogenous cancer cells to the respective reprogrammed chemo-resistance cancer cells (back to the lineage from which the tumor arose) can reveal a reliable chemo-resistance-specific epigenetic signature that is fully independent of its genetic aberrance. Here, we hypothesized a research work to identify the epigenetic control responsible for chemotherapeutic drug resistance by cellular reprogramming of cancer cells.

Presentation of the hypothesis

On the basis of three major facts including (1) epigenetics play an important role in chemo-resistance [27,32–34]; (2) cellular reprogramming resets/erases the existing epigenetic signature [29,35–37] and (3) epigenetic-heterogeneity co-exist in tumor cell populations [28,38–40]; we will attempt to identify epigenetic signatures involved in chemo-resistance by comparing chemo-sensitive cancer cells with the respective reprogrammed chemo-resistant cancer cells. We believe that, following transient reprogramming of a cancer cell, we can produce homogenous colonies with similar epigenetic modifications. Lineage specification of this colony will produce cells with ancestral epigenetic marks. Drug-resistant cells obtained from these cells represent an ideal way to obtain precise epigenetic marks contributing chemo-resistance by comparison with ancestral drug-sensitive cancer cells (Fig. 1). Since cancer cells are heterogeneous in nature, our hypothesis enables the selection of homogenous colonies

Briefly, we will explore the epigenetic control to validate the genes responsible for chemo-resistance by comparing drug-sensitive homogenous cancer cells with the respective reprogrammed chemo-resistance cancer cells via cellular reprogramming.

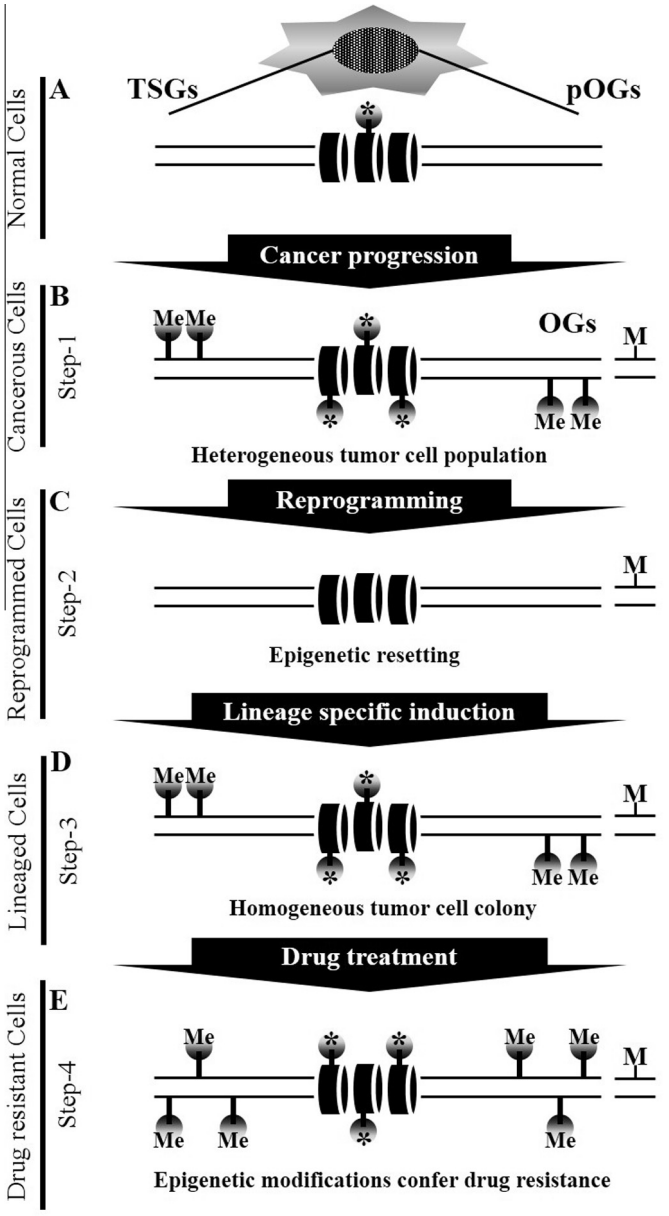

Fig. 1. The epigenetic signature of genome at different cellular stage: (A) in normal cell, generally, tumor suppressor genes (TSGs) are hypo-/un-methylated while oncogenes (OGs) are presents as protooncogenes (pOGs). (B) During cancer progression normal cell undergoes various epigenetic modulations such as hypo-/hyper-methylation of TSGs, and/or activation of OGs, several histone modifications as well as several genetic modifications (M). (C) Reprogramming of cancer cell erases/or reset epigenetic modifications while it unaffected genetic modifications. (D) Lineage specification will generate the homogenous cancer cell colonies with similar epigenetic marks. (E) Again cell undergoes various epigenetic modifications conferring drug resistance after drug treatment.

Testing the hypothesis

The selected cancer cell (Step-1, Fig. 2) will be reprogrammed using iPSC generating chemicals according to the manufacturer's protocols. Transient transfection or mRNA induced cellular reprogramming will be preferred over stable transfection or transduction, since it will not introduce foreign DNA segment into the