Distinct Histone Remodeling Defines Early Stress-induced Drug Tolerance in Cancer

Introduction

Resistance to chemotherapy and targeted therapies is a major problem for cancer treatment. Acquired drug resistance is not only dependent on somatic mutations or drug efflux suggestive of alternative mechanisms like epigenetic changes and chromatin remodeling. We recently have identified early stress-induced multidrug-resistant cancer cells termed induced drug tolerant cells (IDTCs). Different cancer types may share common features following an early innate stress induced response towards exposure to drugs leading to acquired permanent drug resistance through epigenetic remodeling.

Aims:
- To characterize Induced Drug Tolerance Cells (IDTCs) in different cancer types.
- To identify underlying mechanisms for this transition.
- To target specific epigenetic modifications and their functional analysis to prevent the formation of IDTC mediated acquired drug resistance.

Results

A common stress induced transition of cancer cells into IDTCs

Conformities in overall gene expression in IDTCs

CpG sites methylation is not global

Figure 1: A) Drug optimization and relative survival of the different cancer cells. B) Multidrug resistance potency of IDTCs. C) Distinct morphology of IDTCs D) Higher expression of the IDTC marker CD271. E) Hyper-phosphorylation of key signaling proteins in response to different stress in IDTCs compared to parental cells. F) Reverse Phase Protein Array (RPPA) confirming the hyper activation of the signaling cascades.

IDTCs are characterized by distinct histone modifications

Global histone profiling

Figure 2: A) Altered profile of three distinct histone marks, H3K4me3, H3K27me3 and H3K9me3 in IDTCs. B) In other stress condition; nutrient starvation. C) Drug holiday dynamically modulate the histone modifications and D) Induce sensitivity to the treatment.

Figure 3: A) Hierarchical clustering of differential gene expression. B) A volcano plot shows the overall up and down regulated genes. C) Pathway enriched for each of the IDTCs compared to parental cells.

Figure 5: A) Distribution of the histone marks in the IDTC compare to control. B) Histone marking on a subset of downregulated genes represented as polyclamp repressive domains (PRDs) C) Overlapping of the different expressed genes and histone modifications in IDTC.

Figure 7: A) shSETDB1/2 results in reduction of H3K9me3. B) H3K9me3 demethylase from Match-patient data. C) shSETDB1/2 restores drug sensitivity.

Figure 8: A) Stress induce cancer cells to undergo a dynamic histone reprogramming with the increase of repressive histone mark H3K9me3 and decrease of active mark H3K4me3 and repressive mark H3K27me3. Upon drug treatment silenced SETDB1/2 cancer cells reprogram their histone modifications which are sensitive to other drugs.

Conclusion

- Early Drug resistance pattern are similar in different cancers.
- Histone Modifications are generic for any stress.
- Drug holiday modulates epigenetic reprogramming.
- Global increase of H3K9me3 and decrease of H3K4me3 mark characterizes the IDTC which is independent of DNA methylation.
- Increment of H3K9me3 and decrease of H3K4me3 mark resulting transcriptional repression of subset of genes.
- Knockdown of SETDB1/2 restores drug sensitivity.

References

3. Oncogene, doi:10.1038/onc.2014.372