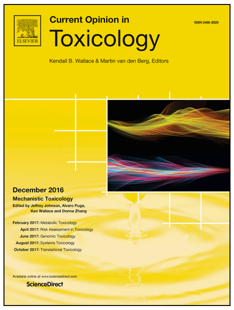

Epigenetics Druggable Targets for Anti-cancer Therapies

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PII: S2468-2020(17)30050-5
DOI: 10.1016/j.cotox.2017.10.010
Reference: COTOX 93

To appear in: *Current Opinion in Toxicology*

Received Date: 19 April 2017
Revised Date: 16 October 2017
Accepted Date: 16 October 2017

Please cite this article as: K. Datta, K. Kolaja, Epigenetics Druggable Targets for Anti-cancer Therapies, *Current Opinion in Toxicology* (2017), doi: 10.1016/j.cotox.2017.10.010.

Epigenetics Druggable Targets for Anti-cancer Therapies.

(Short Title: Epigenetics in Cancer and Therapies)

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Abstract

Epigenetic alterations of a cell are manifested through various mechanisms including DNA methylation, histone modification, nucleosome remodeling and other non-coding mediated pathways. An abnormal expression pattern or genomic alterations in above-mentioned epigenetic regulators can lead to the induction and maintenance of various cancers. Several protein complexes which are known to manipulate these epigenetic regulators alterations, consequently contribute in carcinogenic processes. Therefore, several protein complexes associated DNA methylation and histone modification became druggable targets for cancer treatment. A few epigenetic agents have been approved for cancer treatment. Toxicological profiles of these approved epigenetic agents include hematological and gastrointestinal effects and/or alteration of cardiac electrical properties leading to the prolongation of QTc interval (a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle, corrected for heart rate). Also, these epigenetic agents pose potential risk to fertility and embryofetal development in humans, likely due to their pharmacologic activity and/or antiproliferative effects. Additional safety concerns related to therapeutic manipulation of epigenetic regulation include reports of viral reactivation in humans and potential deleterious effects on germ cell homeostasis and possible inherited, transgenerational effects. This article presents a simple overview of various covalent modifications of DNA and histone, druggability of these modifications in the context of cancer treatment, known safety profiles of epigenetic drugs approved for cancer treatment and potential risks associated with therapeutic manipulation of epigenetic regulation.

Key words: Covalent modification; DNA; Histone; Cancer; Epigenetic agents; Hematological and Gastrointestinal effects; Viral reactivation; Transgenerational inheritance

Background

Epigenetics (which means “above, outside or around genetics”) refers to potentially heritable traits in gene expression associated with modifications of chromatin that do not alter the primary DNA sequence[1]. In short, these epigenetic alterations can confer phenotypic changes without genotypic changes. Epigenetic alteration of a cell is manifested through DNA methylation, histone modification, nucleosome remodeling and other non-coding mediated pathways including RNA interference through micro-RNAs. These epigenetic modifications are responsible for regulation of normal cellular processes such as cellular differentiation and maturation, are part of the pluripotency seen in early development and critical for cellular