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Deep Insight Section

DNA methylation in cancer

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Abstract

Deep insight on DNA methylation in cancer.

Almost every cell in a human organism share the exact same DNA sequence, still it exist more than 200 different cell types that have very distinct functions (e.g fibroblast, neuron, pancreatic cell...). Epigenetic mechanisms participate to instruct cells to acquire and maintain a specific identity. An operational definition of epigenetics is "an epigenetic trait is a stably heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence" (Berger et al., 2009). In other words epigenetic modifications (marks) modulate gene expression mainly by changing the access to the genetic information. A major modification is DNA methylation, the first epigenetic mark to be identified, and the most studied (Baylin and Jones, 2011). DNA methylation is heritable, does not alter the DNA sequence and is the most stable mark. Its role is critical in normal development and defects in DNA methylation pattern is systematically observed in cancer cells.

I- What is DNA methylation?

DNA methylation is a chemical modification (a methyl group) of the DNA that does not alter the information coded by the DNA but it participates to the modulation of gene expression. In mammals DNA methylation occurs on position 5 of cytosine (C) mainly upstream of guanine (G) in the DNA double-helix, the so-called **CpG dinucleotide**. This reaction is catalysed by the DNA methyltransferase enzymes (**DNMT**) that uses the *S*-adenosyl-L-methionine (AdoMet) as methyl donor leading to 5-methylcytosine (5-mC) (Figure 1).

DNMTs are a well-conserved protein family including DNMT1 and DNMT3 that can be distinguish by their main function. DNMT1 (Bestor et al., 1988), which as a high preference for hemi-methylated DNA, is in charge of the "maintenance" of DNA methylation pattern through cell divisions by copying the DNA methylation pattern on the newly synthesized strand.

Accordingly, DNMT1 is the most expressed in somatic cells, particularly at the S phase (Robertson et al., 2000; Hermann et al., 2004) (Figure 2). DNMT3A and DNMT3B are involved in *de novo* DNA methylation that occurs essentially during embryonic development, right after implantation and also during the male and female gametogenesis (Kafri et al., 1992; Okano et al., 1999). DNMT3L is a non-catalytic co-factor for DNMT3A and B that enhance their activity.

Beside DNA methylation, other DNA modification have been reported, 5-hydroxymethylcytosine (5hmC), 5-formylcytosine (5fC) and 5-carboxylcytosine (5caC), and are currently widely studied in particular for their role in active DNA demethylation (Franchini et al., 2012; Fu and He, 2012).

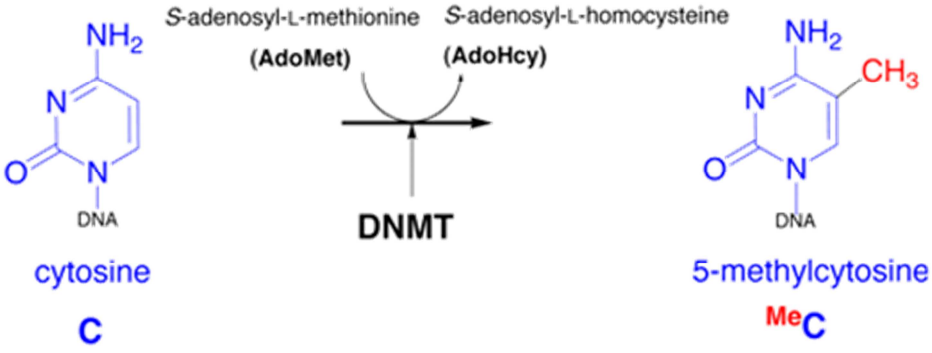

Figure 1. The DNA methyltransferase (DNMT) catalyses the methylation reaction.

II- Where is DNA methylation located?

In the human genome, CpGs dinucleotides are not randomly distributed but are regrouped in CpG islands. Actually, CpGs are under-represented in the genome (1% versus 4% expected) due to the chemical instability of the 5-mC that is spontaneously, but sporadically, converted into thymine (T) by deamination inducing a C to T transition (Schorderet and Gartler, 1992). However, some parts of the genome are enriched in CpGs and show dense DNA methylation:

- **Repeated sequences** (LINE and SINE retrotransposons, satellite DNA at centromeres) that represent near half of the genome are the major site of DNA methylation (Yoder et al., 1997).
- In human, around 65% of genes contain in their promoter (including first exons) **CpG islands**. These islands have been defined by regions of at least 200 base pairs, containing more than 55% of GC and a ratio between the observed CpGs observed and the expected CpGs higher than 0.65 (Gardiner-Garden and Frommer, 1987; Bestor et al., 1988; Takai and Jones, 2002).

Importantly, most of these CpG islands are not methylated in somatic cells.

Those that harbour DNA methylation are related to tissue-specific and imprinting genes and have an important role in defining the identity of the cell.

III- What is the role of DNA methylation?

DNA methylation is essential for normal embryonic development. Mice Knock-Out for DNMT1, 3A and 3B lead to early embryos death (8.5 to 10.5 dpc) or a few weeks after birth (Li et al., 1992; Okano et al., 1999).

In human, the ICF syndrome (Immunodeficiency, Centromere instability, Facial anomalies) is a rare autosomal recessive disease caused by mutations in DNMT3B gene.

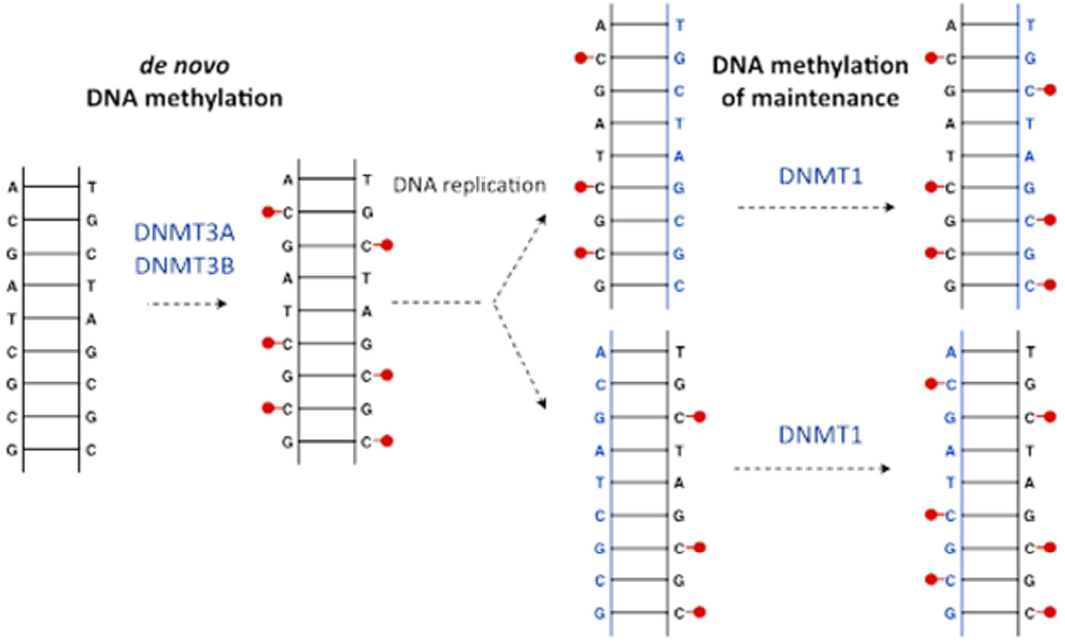

Figure 2. Role of the DNMTs. DNMT1 is mainly involved in DNA methylation maintenance while DNMT3A and DNMT3B are *de novo* methyltransferases. The methyl group on the CpG site is indicated by a red lollipop.

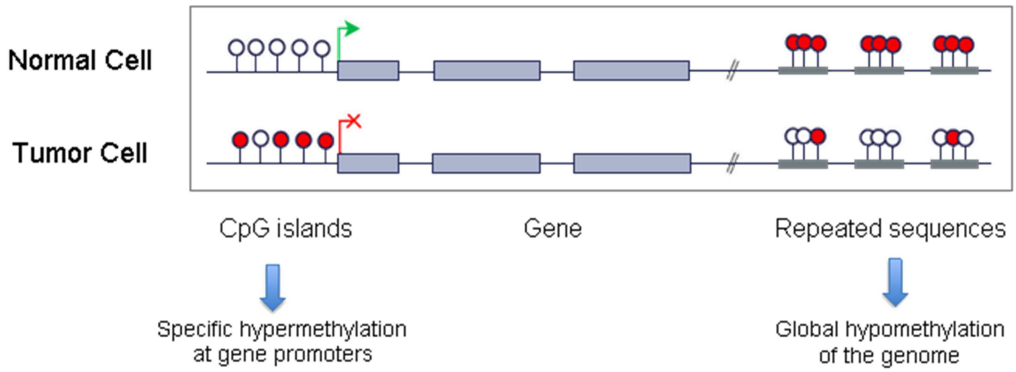

Figure 3. Aberrant DNA methylation profile in cancer cells. In tumor cells, a global loss of DNA methylation at repeated sequences leading to global hypomethylation of the genome is observed together with DNA hypermethylation at specific sites, such as tumor suppressor genes promoters, inducing the silencing the corresponding gene. White lollipop: non-methylated CpG, red lollipop: methylated CpG.

It is characterized by loss of centromeric methylation and genome instability (Hansen et al., 1999). Indeed DNA methylation has a critical role in **genome integrity by repressing transcription at repeated sequences**, including highly mutagenic retrotransposon elements.

When located in promoters, CpG island DNA hypermethylation is also associated with a repressed chromatin and thus transcription inhibition (Iguchi-Ariga and Schaffner, 1989; Watt and Molloy, 1988; Prendergast and Ziff, 1991; Clozel et al., 2013).

Genes located downstream are silenced although their genomic sequence is intact. In differentiated cells, **promote DNA methylation is a common way to shut down the expression of genes** that are not implicated in the specific function of a liver cell, retina cell, neuron...

DNA methylation is also involved in the establishment and maintenance of **genomic imprinting** and, in female cells, **X-chromosome inactivation**. In all these cases, DNA methylation is a transcriptional repressor.

In other contexts like in gene bodies, DNA methylation can play an opposite role and rather be associated with an active transcription (Ball et al., 2009).

Finally it can be also involved in splicing and in the silencing of alternative promoters.

IV- DNA methylation & cancer

It has been now established that aberrant DNA methylation plays a crucial role, together with genetic alterations, in tumorigenesis and tumor maintenance.

1. Aberrant DNA methylation pattern in cancer cells

In tumors, a global DNA hypomethylation is associated with a local DNA hypermethylation of specific loci (Figure 3). This seems very contradictory but theses two phenomena act at different sites of DNA methylation and participate both to cancer formation.

2. Global DNA hypomethylation of the genome

One of the first epigenetic alterations found in cancer cells was a global decrease in DNA methylation.

Repeated sequences, which are highly methylated, are hypomethylated, triggering transcriptional re-activation of parasitic DNA sequences that can randomly integrated into the genome contributing to the high genetic instability of cancer cells (Dante et al., 1992; Alves et al., 1996; Howard et al., 2008).

Moreover examples of loss of DNA methylation have been reported at gene promoters leading to their re-expression. This is the case of *MAGE* gene family that are normally repressed in all cell types at the exception of testicular cells (De Smet et al., 1999). Oncogenes such as *R-RAS*, *RHOB* and *ELK1* have also been described as re-expressed in gastric cancers following demethylation of their promoters (Nishigaki et al., 2005). All these events participate to tumorigenesis at early steps of the disease.

3. Localized DNA hypermethylation

In the human genome, CpG islands are mainly located in gene promoters and are the targets of **DNA hypermethylation** in cancers. It is estimated that 5 to 10% of promoters are hypermethylated in cancer leading to the silencing of downstream genes (Bird, 2002). Mainly this process concerns tumor suppressor genes (TSG) thus favoring cancer development.

The first TSG that was described to be silenced by hypermethylation was Retinoblastoma (*Rb*) (Greger et al., 1989), involved in the control of the cell cycle. Next a battery of hypermethylated genes were found to be involved in crucial processes such as DNA repair (*BRCA1*) (Esteller et al., 2000), cell proliferation (*CDKN2A*) (Merlo et al., 1995), cell adhesion (*CDH1*) (Graff et al., 1995), angiogenesis (*VHL*) (Herman et al., 1994) and other essential

functions. Interestingly, each cancer has a DNA methylation profile that can be used as signature to develop diagnostic biomarkers (Costello et al., 2000; Esteller et al., 2001; Paz et al., 2003). The first commercial DNA methylation tests for diagnosis are based on the detection of Septin9 hypermethylation in blood plasma for colon cancer (ColoVantage® test) and GSTPI hypermethylation in urine for prostate cancer (test by LabCorp). In addition, promoter DNA hypermethylation can be used to predict the response to treatment, such as *MGMT* hypermethylation in glioblastoma patients for temozolomide treatment (test by MDxHealth).

Since loss of TSG expression by aberrant DNA methylation gives to tumor cells a strong proliferative advantage, DNA hypermethylation could be set up randomly and only DNA methylation profiles conferring a selective advantage would be maintained in the tumor (as for genetic mutations). However several observations pointed out that cancer DNA hypermethylation can be an instructive mechanism. DNA methylation is an early event of the tumor formation (Issa, 2004; Feinberg et al., 2006; Troyer et al., 2009). Short DNA sequences are found enriched at hypermethylated promoters suggesting a sequence-specific targeting (Feltus et al., 2003; Feltus et al., 2006; Keshet et al., 2006). Interestingly, entire chromosome regions can be subject to the same epigenetic repression (LRES: Long-Range Epigenetic Silencing) (Frigola et al., 2006; Coolen et al., 2010) or reactivation (LREA: Long-Range Epigenetic Activation) (Bert et al., 2013). Hypermethylation can cluster on chromosomes, which are delimitated by insulator proteins like CTCF (Witcher and Emerson, 2009); LINE and SINE retrotransposons sequences protect adjacent promoters from DNA methylation (Estécio et al., 2010); polycomb target genes are predispose to hypermethylation (Ohm et al., 2007; Schlesinger et al., 2007; Widschwendter et al., 2007); and non-coding RNAs can also direct specifically DNA hypermethylation by interacting with DNMT (Di Ruscio et al., 2013). It seems that many parameters (gene localisation, promoter sequence, transcription activity, developmental program...) are, all together, important to define if a promoter will be subjected to DNA methylation during tumorigenesis.

V- Targeting DNA methylation in cancers

The study of the cancer epigenome - the ensemble of epigenetic marks on the genome - is of great interest as it can help clinical diagnosis, prognostic and treatment strategies. Today several consortium are built to determine the human epigenomes in several contexts, such as the Human Epigenome Project (HEP, at http://www.epigenome.org/) that aims at measuring the DNA methylation profile in all major tissues or such as The Cancer Genome Atlas (TCGA at https://tcga-data.nci.nih.gov/tcga/tcgaHome2.jsp) that determine the genetic and epigenetic profiles in cancers.

Noteworthy, by altering DNA methylation cells modulate at once several biological processes and signaling cascades, making its targeting a therapeutic advantage (Azad et al., 2013).

VI- Present and the future of DNA methylation cancer therapy

In addition, contrary to genetic mutations, epimutations are reversible and thus offer interesting therapeutic perspectives.

By targeting DNA methylation, cells are reprogrammed; reexpression of TSG can induce cell arrest, differentiation and death, but also sensitivity to apoptosis, immuno-response and drug treatment.

An example is the reversal of the resistance to doxorubicine in diffuse large B-cell lymphoma (DLBL) by low-doses of DNMT inhibitors (Clozel et al., 2013).

It exists two classes of DNMT inhibitors (**DNMTi**): the nucleoside analogues that are incorporated into nucleic acids and form a covalent complex with the enzyme, and the non-nucleoside inhibitors that present different mechanisms of inhibition.

1. DNMTi: Nucleoside analogues and anti-cancer therapy

Nucleoside analogues are based on ribose or deoxyribose analogs of cytidine, in particular 5-aza-cytidine (5aza) and 5-aza-2'deoxycytidine (5azadC) are used in clinics for the treatment of myeolodysplastic syndromes (MDS) and acute myeloid leukemia (AML) (**FDA approval** in 2004 and 2006, respectively, for MDS, AML and CMML (chronic myelomonocytic leukemia) (Figure 4).

In cells, these compounds are metabolized by kinases to convert them into nucleotides that are incorporated into RNA (5aza) or into DNA (5azadC and 5aza after conversion of the ribose in deoxyribose). Since these compounds need to be integrated into the DNA to be active, they are particularly efficient in highly proliferative cells like cancer ones.

During the catalytic reaction, DNMTs binds covalently to position 6 of the cytosine ring and after transfer of the methyl group a β-elimination reaction frees the enzyme (Figure 4B). In the case of the aza-nucleoside the β-elimination cannot occur and the enzyme is trapped on the DNA forming a suicide complex (Figure 4C), and eventually it is degraded by the proteasome. Because of their mechanism of action, these compounds are not selective towards the different DNMTs and thereby induce a global decrease of DNA methylation.

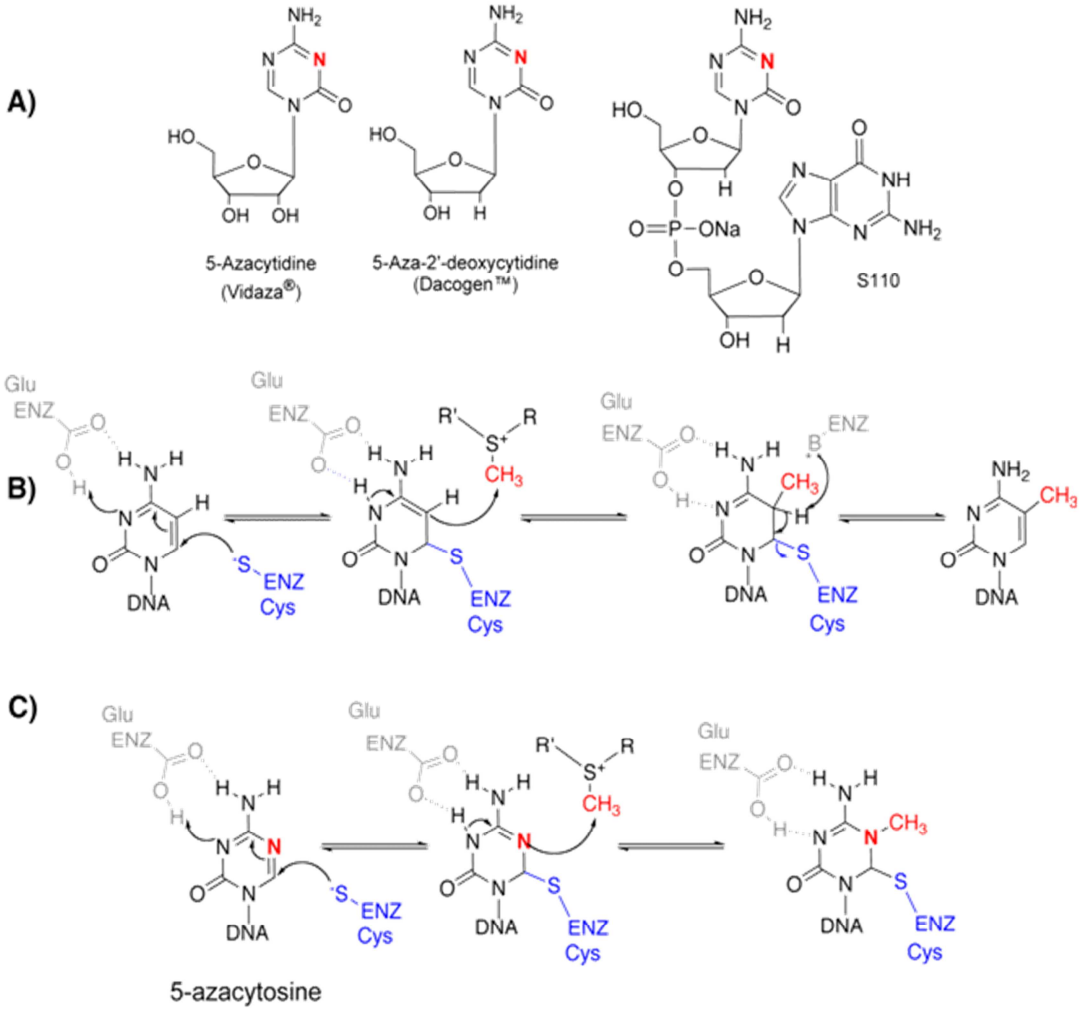

Figure 4. A) Chemical structure of 5-aza-cytidine, 5-aza-2' deoxycytidine, prodrug SGI110. **B)** Catalytic reaction by DNMTs. **C)** Inhibition by 5azacytosine in DNA.

In addition, 5aza (Vidaza) and 5azadC (Dacongen) are limited to hemotological cancer because of their chemical instability.

Recently, a prodrug, a 5azadCpdG analog, SGI110 (developed by Astex) (Chuang et al., 2010), is in clinical trials for haematological diseases, and solid cancers in combination; the results are encouraging. Indeed, very promising results have been obtained with the 5aza-nucleosides in combination with HDAC inhibitors (Juergens et al., 2011) and/or when used to restore chemosensitivity to anticancer treatments (Clozel et al., 2013; Vijayaraghavalu et al., 2013; Wrangle et al., 2013). Still, these molecules are non-specific toward the DNMTs, act on the whole genome, are chemically instable and have secondary effects in patients (renal toxicity, myelotoxicity), therefore there are continuous efforts aiming at finding non-nucleoside inhibitors.

2. Non-nucleoside inhibitors for DNMT selectivity

Non-nucleoside inhibitors share the common feature of not being incorporated in DNA. However they inhibit the catalytic reaction by different mechanisms of action: they can compete with the cofactor, the AdoMet, the DNA substrate or bind to allosteric sites. Today many are described, of different nature, but few are well characterized for their mechanism of action or their selectivity towards a specific DNMT (for review Fahy et al., 2012; Gros et al., 2012). For example, SGI-1027 belongs to a family of minor groove DNA binders developed by Denny and collaborators (Datta et al., 2009) and has been shown to inhibit DNA methylation in enzymatic tests and in cancer cells. We developed two families of DNMT inhibitors: procainamide conjugates that are selective of DNA methyltransferases versus histone methyltransferases (Halby et al., 2012) and flavanoid derivatives that also inhibit DNA methylation in an *in vivo* model of zebrafish development (Ceccaldi et al., 2011). Since the small molecules identified so far showed less anti-cancer activities than nucleoside analogs and present limited therapeutic interest, we and others have developed high-throughput screening and drug

design strategies to discover new inhibitors (Ceccaldi et al., 2013; Kilgore et al., 2013; Weng et al., 2014).

3. Perspectives in DNMTi

The success of 5aza and 5azad as anti-cancer treatments alone and more recently in combination leads researchers to focus on new compounds with improved bioavaibility and specificity.

Many efforts are also dedicated to better understand the mechanism of action in cancer cells of the azanucleoside and their long-term consequences. There is still an urgent need to find new small molecules specific to each DNMTs to better understand the role of each enzyme in tumorigenesis and cancer maintenance and to decrease the off-targets.

These new drugs will benefit to cancer patients but not only since abnormal DNA methylation pattern is also involved in other pathologies such as autoimmune and neurological disorders.

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