# An epigenetic road map for histone lysine methylation

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This poster is dedicated to the memory of Alan Wolffe, an inspirational and integrative leader for the field of chromatin regulation and epigenetic control.

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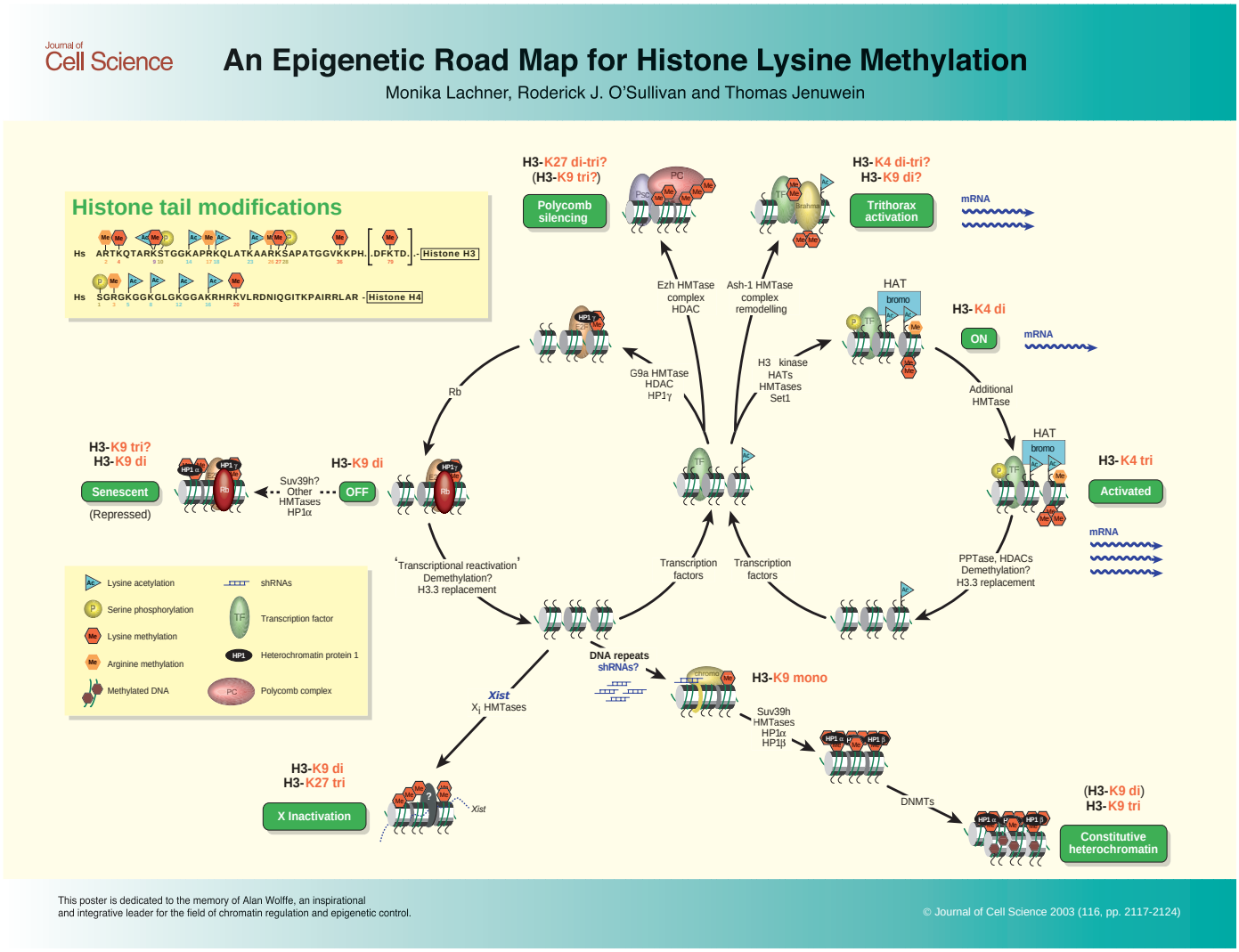
## Introduction

Histone N-termini (tails) undergo diverse post-translational modifications, including acetylation, phosphorylation, methylation, ubiquitination and ADP-ribosylation (van Holde, 1988; Wolffe, 1998). The discoveries of enzymes that perform these modifications and of chromatin-associated proteins that selectively bind to position-specific histone modifications (Strahl and Allis, 2000; Jenuwein and Allis, 2001) reveals that modified histone N-termini can significantly extend the information potential of the genetic code. Moreover, they appear to index chromatin regions, facilitating epigenetic control, lineage commitment and the overall functional organisation of chromosomes.

Acetylation (Roth et al., 2001) and arginine methylation (Stallcup, 2001) have been linked mainly with transcriptional stimulation. Phosphorylation (Cheung et al., 2000a) instead is a marker for activation of immediate early genes and a signal for mitotic chromatin condensation. Here, we focus on histone lysine methylation. The roles of acetylation, phosphorylation and methylation are summarized in Table 1, and discussion of the interplay between these distinct modifications can be found elsewhere (Zhang and Reinberg, 2001; Berger, 2002; Kouzarides, 2002).

## The complexity of histone lysine methylation

At least five methylatable lysine positions exist in the N-termini of histones H3 (K4, K9, K27, K36) and H4 (K20); another occurs in the histone-fold domain of histone H3 (K79) (Feng et al., 2002; Lacoste et al., 2002; Ng et al., 2002; van Leeuwen et al., 2002). For




*(See poster insert)*

**Table 1. Histone acetylation, phosphorylation and methylation**

| Site | Enzyme | Function | Reference |
|---|---|---|---|
| **Histone H3** | | | |
| R2-Me | CARM1 (*Mm,Hs*) | In vitro methylation site | Chen et al., 1999, Schurter et al., 2001 |
| K4-Me | ??? (*Tt*) | Transcriptional activation | Strahl et al., 1999 |
| | Set1 (*Sc*) | rDNA silencing, telomeric silencing | Briggs et al., 2001, Roguev et al., 2001, Nagy et al., 2002, Bryk et al., 2002 |
| | Set1 (*Sc*) | Transcriptional activation | Bernstein et al., 2002, Santos-Rosa et al., 2002 |
| | SET7/Set9 (*Hs*) | Transcriptional activation | Wang et al., 2001a, Nishioka et al., 2002a, Zegerman et al., 2002 |
| | Trx/MLL (*Dm,Hs*) | Trithorax activation | Czermin et al., 2002, Milne et al., 2002, Nakamura et al., 2002 |
| | Ash1 (*Dm*) | Trithorax activation (in concert with H3-K9 and H4-K20 methylation) | Beisel et al., 2002 |
| K9-Ac | SAGA (*Sc*) | Transcriptional activation | Grant et al., 1999 |
| | SRC1 (*Mm*) | Nuclear receptor coactivator | Spencer et al., 1997 |
| K9-Me | Suv39h1 (*Mm*) | Pericentric heterochromatin | Rea et al., 2000, Lachner et al., 2001, Peters et al., 2001 |
| | Suv39h2 (*Mm*) | Pericentric heterochromatin | O'Carroll et al., 2000, Lachner et al., 2001, Peters et al., 2001 |
| | Su(var)3-9 (*Dm*) | Dominant PEV modifier | Czermin et al., 2001, Schotta et al., 2002 |
| | Clr4 (*Sp*) | Centromeric/mating-type silencing | Bannister et al., 2001, Nakayama et al., 2001 |
| | Dim5 (*Nc*)<br>KRYPTONITE (*At*)<br>Suv39h1 (*Mm*)<br>Suv39h2 (*Mm*) | DNA methylation<br>DNA methylation<br>DNA methylation<br>DNA methylation | Tamaru and Selker, 2001<br>Jackson et al., 2002<br>B. Lehnertz et al., unpublished<br>B. Lehnertz et al., unpublished |
| | SUV39H1 (*Hs*) | Rb-mediated silencing | Nielsen et al., 2001, Vandel et al., 2001 |
| | G9a (*Mm*) | Imprinting | Xin et al., 2003 |
| | G9a (*Mm*) | Transcriptional repression | Tachibana et al., 2001, Tachibana et al., 2002 |
| | G9a (*Hs*)<br>Eu-HMTase1 (*Hs*) | Transcriptional repression | Ogawa et al., 2002 |
| | Eset/SETDB1 (*Mm,Hs)* | Transcriptional repression | Yang et al., 2002, Schultz et al., 2002 |
| | E(z)/EZH2 (*Dm,Hs*) | Polycomb repression | Czermin et al., 2002, Kuzmichev et al., 2002 |
| | Ash1 (*Dm*) | Trithorax activation (in concert with H3-K4 and H4-K20 methylation) | Beisel et al., 2002 |
| | ??? (*Mm,Hs*) | X-chromosome inactivation | Boggs et al., 2002, Peters et al., 2002, Heard et al., 2001, Mermoud et al., 2002 |
| S10-P | Snf1 (*Sc*) | Transcriptional activation | Lo et al., 2001 |
| | Jil-1 (*Dm*) | Transcriptional upregulation of male X-chromosome | Jin et al., 1999, Wang et al., 2001b |
| | Rsk2 (*Mm,Hs*)<br>Msk1 (*Mm*) | Transcriptional activation of immediate early genes (in concert with H3-K14 acetylation) | Sassone-Corsi et al., 1999, Thomson et al., 1999, Cheung et al., 2000b, Clayton et al., 2000 |
| | Ipl1/AuroraB (*Sc,Ce*) | Mitotic chromosome condensation | Wei et al., 1999, Hsu et al., 2000 |
| | NIMA (*An*) | Mitotic chromosome condensation | De Souza et al., 2000 |
| K14-Ac | Gcn5 (*Tt,Sc,Mm*) | Transcriptional activation | Brownell et al., 1996, Kuo et al., 1996 |
| | $TAF_{II}230$ (*Dm*)<br>$TAF_{II}250$ (*Hs*) | Transcriptional activation | Mizzen et al., 1996 |
| | p300 (*Hs*) | Transcriptional activation | Schiltz et al., 1999 |
| | PCAF (*Hs*) | Transcriptional activation | Schiltz et al., 1999 |
| | SRC1 (*Mm*) | Nuclear receptor coactivator | Spencer et al., 1997 |
| R17-Me | CARM1 (*Mm,Hs*) | Transcriptional activation | Chen et al., 1999, Schurter et al., 2001, Ma et al., 2001, Bauer et al., 2002 |
| | CARM1 (*Mm,Hs*) | Transcriptional activation (in concert with H3-K18/23 acetylation) | Daujat et al., 2002 |
| K18-Ac | SAGA (*Sc*)<br>Ada (*Sc*) | Transcriptional activation | Grant et al., 1999 |
| | p300 (*Hs*) | Transcriptional activation | Schiltz et al., 1999 |
| | CBP (*Hs*) | Transcriptional activation (in concert with H3-R17 methylation) | Daujat et al., 2002 |
| K23-Ac | SAGA (*Sc*) | Transcriptional activation | Grant et al., 1999 |
| | CBP (*Hs*) | Transcriptional activation (in concert with H3-R17 methylation) | Daujat et al., 2002 |

**Table 1. Continued**

| | | | |
|---|---|---|---|
| R26-Me | CARM1 (*Mm*,*Hs*) | In vitro methylation site | Chen et al., 1999, Schurter et al., 2001 |
| Site | Enzyme | Function | Reference |
| K27-Me | G9a (*Mm*) | Transcriptional repression | Tachibana et al., 2001, Tachibana et al., 2002 |
| | E(z)/EZH2 (*Dm*,*Hs*) | Polycomb repression | Czermin et al., 2002, Cao et al., 2002, Müller et al., 2002, Kuzmichev et al., 2002 |
| | EZH2 *(Hs)* | Progression of human prostate cancer | Varambally et al., 2002 |
| | Ezh2 (*Mm*) | Early B-cell development, IgH rearrangement | Su et al., 2003 |
| | Ezh2 (*Mm*) | X-chromosome inactivation | Wang et al., 2001c, Mak et al., 2002, Silva et al., 2003, Plath et al., 2003 |
| S28-P | Aurora-B (*Mm*,*Hs*) | Mitotic chromosome condensation | Goto et al., 1999, Goto et al., 2002 |
| K36-Me | Set2 (*Sc*) | Gene repression | Strahl et al., 2002 |
| K79-Me | Dot1/DOT1L (*Sc*,*Hs*) | Telomeric silencing, pachytene checkpoint | van Leeuwen et al., 2002, Lacoste et al., 2002, Ng et al., 2002, Feng et al., 2002 |
| **Histone H4** | | | |
| S1-P | ??? | ??? | van Holde, 1988 |
| R3-Me | PRMT1 (*Hs*) | Transcriptional activation | Strahl et al., 2001, Wang et al., 2001d |
| K5-Ac | Hat1 (*Tt*,*Dm*,*Hs*) | Histone deposition | Sobel et al., 1995, Kleff et al., 1995, Parthun et al., 1996 |
| | Esa1/NuA4 (*Sc*) | Cell cycle progression | Smith et al., 1998, Clarke et al., 1999, Allard et al., 1999 |
| | ATF2 (*Hs*,*Mm*) | Sequence-specific transcription factor | Kawasaki et al., 2000 |
| | p300 (*Hs*) | Transcriptional activation | Schiltz et al., 1999 |
| K8-Ac | ATF2 (*Hs*,*Mm*) | Sequence-specific transcription factor | Kawasaki et al., 2000 |
| | PCAF (*Hs*) | Transcriptional activation | Schiltz et al., 1999 |
| | p300 (*Hs*) | Transcriptional activation | Schiltz et al., 1999 |
| K12-Ac | Hat1 (*Sc*) | Histone deposition | Sobel et al., 1995, Kleff et al., 1995, Parthun et al., 1996 |
| K16-Ac | MOF(*Dm*) | Transcriptional upregulation of male X-chromosome | Akhtar and Becker, 2000b, Smith et al., 2000 |
| | ATF2 (*Hs*,*Mm*) | Sequence-specific transcription factor | Kawasaki et al., 2000 |
| K20-Me | Pr-SET7/Set8 (*Hs*,*Dm*) | Transcriptional silencing mitotic condensation | Nishioka et al., 2002b, Fang et al., 2002, Rice et al., 2002 |
| | Ash1 (*Dm*) | Trithorax activation (in concert with H3-K4 and H3-K9 methylation) | Beisel et al., 2002 |

Species abbreviations: *Hs*, *Homo sapiens*; *Mm*, *Mus musculus*; *Dm*, *Drosophila melanogaster*; *At*, *Arabidopsis thaliana*; *Tt*, *Tetrahymena thermophila*; *Sp*, *Schizosaccharomyces pombe*; *Sc*, *Saccharomyces cerevisiae*; *Nc*, *Neurospora crassa*; *An*, *Aspergillus nidulans*; *Ce*, *Caenorhabditis elegans.*

clarity, we focus on H3-K4, H3-K9 and H3-K27 methylation to illustrate the general principles and complexities involved.

The mammalian Suv39h enzymes and their *S. pombe* homologue, Clr4, were the first histone lysine methyltransferases (HMTases) identified (Rea et al., 2000). The conserved SET-domain of the Su(var)3-9-related HMTases catalyzes the methylation of H3-K9, creating a high-affinity binding site for the chromodomain of heterochromatin protein 1 (HP1) proteins (Lachner and Jenuwein, 2002). Other methylatable lysine positions might also be marked by position-specific SET-domain HMTases for methyl-binding chromodomain proteins. The human and mouse genomes each encode ≥50 predicted SET-domain proteins (Kouzarides, 2002) and ≥30 chromodomain-containing sequences (A. Schleiffer and F. Eisenhaber, personal communication). By contrast, *S. pombe* has only ~10 putative SET domain HMTases, and *S. cerevisiae* has not more than seven (Briggs et al., 2001). Lysine residues are mono-, di- and tri-methylated in vivo (Paik and Kim, 1971; van Holde, 1988; Waterborg, 1993). A progressive conversion towards tri-methylation could contribute to the apparent stability of histone lysine methylation and is ideally suited to imparting additional layers of combinatorial control, which might allow both short-term and long-term chromatin imprints.

The poster shows the dynamic cycle of histone lysine methylation in transcriptional stimulation or repression. ‘Exit routes’ from this cycle reveal more extended reprogramming of the chromatin structure – for example, during cellular senescence, Polycomb-mediated transcriptional memory, X chromosome inactivation and constitutive heterochromatin formation. In this ‘road map’, the various destinations for a chromatin region are indicated by road signs that reflect distinct methylation positions and states.

## Transcriptional regulation – going around with H3-K4 and H3-K9

In euchromatic regions, binding of transcription factors to specific promoter/enhancer sequences is the initiating step in altering a naive chromatin template. If positively acting complexes prevail, promoter-proximal nucleosomes sequentially adopt an activation-specific modification profile (Urnov and Wolffe, 2001; Zhang and Reinberg, 2001; Berger, 2002; Daujat et al., 2002). Fully activated promoters appear to be enriched in tri-methylated H3-K4 (Santos-Rosa et al., 2002); basal transcription correlates with H3-K4 di-methylation, although the methylation potential of the HMTases involved needs to be defined (Briggs et al., 2001; Nishioka et al., 2002a; Wang et al., 2001a; Santos-Rosa et al., 2002).

H3-K9 methylation, by contrast, is present mainly in silenced chromatin domains (Noma et al., 2001; Litt et al., 2001), and the 'activated genome' of *S. cerevisiae* exhibits abundant H3-K4 methylation but lacks apparent H3-K9 di-methylation (Briggs et al., 2001). Recruitment of several H3-K9-specific HMTases induces gene repression within euchromatin (Tachibana et al., 2001; Nielsen et al., 2001; Vandel et al., 2001; Ogawa et al., 2002; Schultz et al., 2002; Tachibana et al., 2002; Yang et al., 2002). G9a and a closely related enzyme appear to be euchromatic HMTases that form complexes with HP1γ and a subset of E2F transcription factors (Ogawa et al., 2002). These enzymes might, by default, repress target promoters that fail to recruit additional activating complexes.

In proliferating cells and for G9a-mediated in vivo methylation, the repressive signal appears to be primarily H3-K9 di-methylation (Tachibana et al., 2002) (A. H. Peters, S. Kubicek, L. Perez-Burgos et al., unpublished), although in vitro G9a methylates both H3-K9 and H3-K27. Differences between H3-K9 di- and tri-methylation patterns could underpin the more robust association of inhibitory complexes with the promoters of several cell cycle genes, as cells enter senescence (S. Lowe, personal communication) or have their growth potential restricted by the tumor suppressor Rb, which could recruit additional repressive HMTases (Nielsen et al., 2001).

For histone lysine methylation, no 'direct' demethylase has been described. Although intermediary enzymes could destabilise the amino-methyl bond by oxidation or radical attack (Chinenov, 2002; Falnes et al., 2002; Trewick et al., 2002), reversion of an engaged chromatin region to a more naive state might instead be triggered by transcription-coupled histone replacement, in which the histone H3.3 variant is deposited in place of modified histone H3 (Ahmad and Henikoff, 2002a). This mechanism does not operate in transcriptionally silent domains, which might explain turnover of methylated histones in euchromatic regions while allowing persistence of histone methylation in constitutive heterochromatin (Ahmad and Henikoff, 2002b).

## Polycomb and trithorax – keeping on track with H3-K27 and H3-K4

During differentiation, 'transcriptional memory' maintains the expression status of certain key regulatory genes over many cell division cycles. This depends on the antagonistic function of polycomb (Pc-G) and trithorax (trx-G) group proteins (Orlando and Paro, 1995; Pirrotta, 1998). The Pc-G protein enhancer of zeste [E(z)] contains a SET domain and becomes an HMTase when complexed with another early-acting Pc-G protein, extra sex combs (Esc). The *Drosophila* E(z)-Esc complex (Czermin et al., 2002; Müller et al., 2002) and its mammalian Ezh-Eed counterpart (Cao et al., 2002; Kuzmichev et al., 2002) have an apparent preference for H3-K27 but might also target H3-K9. Ezh/Eed-mediated nucleosome methylation increases in vitro binding of the chromodomain protein polycomb (PC) (Czermin et al., 2002; Kuzmichev et al., 2002). In E(z) mutants, methylation of H3-K27, and probably also H3-K9, is impaired – in a manner suggesting that extended H3-K27 di- and tri-methylation across several nucleosomes (Cao et al., 2002) or dual tri-methylation of H3-K27 and H3-K9 [(Czermin et al., 2002) R. Paro, personal communication] might induce stable recruitment of Pc-G complexes. The E(z) HMTase complex could be developmentally regulated such that a di-methylating activity prepares histones for a tri-methylating activity, which propagates transcriptional memory. Fully defining the in vivo methyl mark(s) involved, however, requires the development of highly specific H3-K27 and H3-K9 antibodies.

Long-term maintenance of active transcriptional states is regulated by trx-G proteins. The trx-G proteins Trx/MLL (Milne et al., 2002; Nakamura et al., 2002) and Ash-1 each contain a SET domain and display HMTase activity. Whereas a Trx complex performs H3-K4 di-methylation (Czermin et al., 2002; Milne et al., 2002; Nakamura et al., 2002), Ash-1 can methylate H3-K4, H3-K9 and probably also H4-K20 (Beisel et al., 2002). Ash-1-mediated methylation apparently prevents binding of the repressive PC and HP1 proteins but facilitates association of the Brahma co-activator (Beisel et al., 2002) – another trx-G protein and a component of nucleosome-mobilising machines. Indeed, H3-K4 methylation can trigger recruitment of the Brahma-related ISWI ATPase (T. Kouzarides, personal communication). Thus, trx-G HMTases may allow propagation of an activated chromatin state by 'neutralising' repressive marks (e.g. H3-K9 and H4-K20 methylation) (Fang et al., 2002; Nishioka et al., 2002b), while simultaneously coupling a positive signal (H3-K4 methylation) with chromatin remodelling.

## X-inactivation – choosing an exit with H3-K9 and H3-K27

Dosage compensation in female mammals involves chromosome-wide inactivation of one X-chromosome (Avner and Heard, 2001). H3-K9 methylation is associated with the inactive X chromosome (Xi) (Boggs et al., 2002; Peters et al., 2002; Heard et al., 2001; Mermoud et al., 2002), but H3-K27 tri-methylation might also be a prominent, if not the major, mark (Silva et al., 2003; Plath et al., 2003) (A. H. Peters, S. Kubicek, L. Perez-Burgos et al., unpublished). Pronounced H3-K27 tri-methylation at the Xi would be consistent with the finding that X-inactivation is independent of Suv39h HMTases and does not require HP1

proteins (Peters et al., 2002). The HMTases that target the Xi, particularly for random X-inactivation, are unidentified. A likely candidate for initiating early methylation imprints is the Ezh-Eed complex, because both Ezh2 (Mak et al., 2002) and Eed (Wang et al., 2001c) accumulate at the Xi during imprinted X-inactivation. However, in contrast to Pc-G-mediated gene silencing, there is no evidence for stable association of PC or other Pc-G complexes at the Xi (Silva et al., 2003). Differences in H3-K27 and H3-K9 methylation could discriminate between Pc-G-dependent repression (extended H3-K27 di- and tri-methylation or a combination of H3-K9 tri- and H3-K27 tri-methylation?) and X-inactivation (a combination of H3-K9 di- and H3-K27 tri-methylation?). Alternatively, the *Xist* RNA could provide an additional signal for recruitment of other, Xi-restricted HMTases and associated silencing complexes. This would be similar to *Xist*-dependent accumulation of BRCA1 (Ganesan et al., 2002) and preclude occupancy by the PC system and HP1 proteins. Subtle differences in the methylation state of lysine positions might also be associated with allele-specific imprinting (Xin et al., 2001; Fournier et al., 2002; Xin et al., 2003).

## Constitutive heterochromatin – a one-way street to H3-K9 tri-methylation?

Unlike euchromatin, constitutive heterochromatin lacks apparent transcription units, and instead contains arrays of satellite repeats (Karpen and Allshire, 1997; Csink and Henikoff, 1998). Such repeats appear to give rise – through the RNAi machinery – to small heterochromatic RNAs (shRNAs) (Volpe et al., 2002; Hall et al., 2002; Partridge et al., 2002; Mochizuki et al., 2002; Taverna et al., 2002). These or other RNAs (Maison et al., 2002) might pair with the underlying DNA sequences and bind to chromodomain-like adaptor proteins (Akhtar et al., 2000a) that could recruit Su(var)3-9-related HMTases (Jenuwein, 2002). The H3-K9 methylation signal would then be stabilised and propagated by 'interlocking' HP1 molecules to form an extended heterochromatic domain (Nakayama et al., 2001; Hall et al., 2002). Furthermore, H3-K9 methylation can trigger DNA methylation in *Neurospora crassa* (Tamaru and Selker, 2001) and *Arabidopsis thaliana* (Jackson et al., 2002), and a similar pathway directs DNA methylation at pericentric satellite repeats in mammals (B. Lehnertz, Y. Ueda, A. A. Derijck et al., unpublished). The combination of histone- and DNA-methylation systems (Fahrner et al., 2002; Nguyen et al., 2002; Fuks et al., 2003) probably stabilises silent chromatin domains, safe-guarding gene expression programmes and protecting genome integrity.

Pericentric heterochromatin is enriched in tri-methylated H3-K9. This profile is selectively abolished upon disruption of Suv39h HMTases, whereas centromeric regions display Suv39h-independent H3-K9 di-methylation (A. H. Peters, S. Kubicek, L. Perez-Burgos et al., unpublished). Interestingly, in Suv39h dn cells, pericentric heterochromatin exhibits significant H3-K9 mono-methylation (A. H. Peters, S. Kubicek, L. Perez-Burgos et al., unpublished). Suv39h HMTases are thus tri-methylating enzymes that can convert intermediary methylation states (mono- or di-methylation) into the apparently more stable tri-methylation end state. Regional H3-K9 tri-methylation at transcriptionally inert chromatin domains therefore appears to be a robust hallmark of constitutive heterochromatin.

## Outlook

The above examples highlight the exquisite complexity and coding potential of histone lysine methylation in epigenetic control. Position- and state-specific methylation antibodies (Santos-Rosa et al., 2002) (A. H. Peters, S. Kubicek, L. Perez-Burgos et al., unpublished) and the solved 3D-structures of several SET domain enzymes (Trievel et al., 2002; Wilson et al., 2002; Zhang et al., 2002; Jacobs et al., 2002; Min et al., 2002) have started to reveal the functions of mono- (SET7/9; Xiao et al., 2003), di- [G9a (Tachibana et al., 2002) (A. H. Peters, S. Kubicek, L. Perez-Burgos et al., unpublished)] and tri-methylating HMTases [Suv39h (A. H. Peters, S. Kubicek, L. Perez-Burgos et al., unpublished)]. Although the 'rules of the road' highlighted in this poster focused on basic mechanisms of transcriptional regulation and chromosome organisation, histone lysine methylation probably affects most chromatin-templated processes – from cell proliferation and tumorigenesis (Varambally et al., 2002) to imprinting, X-inactivation, lineage commitment (Su et al., 2003), aging, stem cell plasticity and the epigenetic reprogramming of the genome.

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