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# Dynamic Histone H3 Incorporation Fuels Metastatic Progression

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## Spotlight

Dynamic Histone H3  
Incorporation Fuels  
Metastatic  
ProgressionIva Simeonova<sup>1,2,3,4</sup>  
and Geneviève Almouzni<sup>1,2,3,4,\*</sup>

Treating metastatic cancers is an ongoing challenge in oncology. A recent paper by [Gomes and colleagues](#) proposes histone H3 variant dynamics as major regulator of cell fate transition during metastasis and suggests histone chaperones as therapeutic targets for invasive carcinoma.

Recent large-scale sequencing of metastatic cancers from more than 10 000 patients represents a major step forward in our understanding of metastatic cancer genomes [1]. However, our knowledge about the dynamic chromatin landscape in metastatic cancers is still very limited. In a recent publication in *Cancer Cell*, Gomes *et al.* [2] provide hints into how extracellular signal regulated kinase (ERK)-dependent metastatic signaling, which is among the most frequently altered pathways in cancer progression, promotes a switch in histone H3 variant incorporation into chromatin to trigger an epigenomic and transcriptional reprogramming towards cancer aggressiveness [2].

Histone variants, the building blocks of chromatin, mark particular regions of the genome in each cell type. This involves incorporation by distinct histone chaperones [3]. The chromatin assembly factor 1 complex (CAF-1) promotes deposition of the replicative H3.1/H3.2 histone variants in a DNA-synthesis-dependent manner, mainly during replication. In contrast, the HIRA chaperone complex

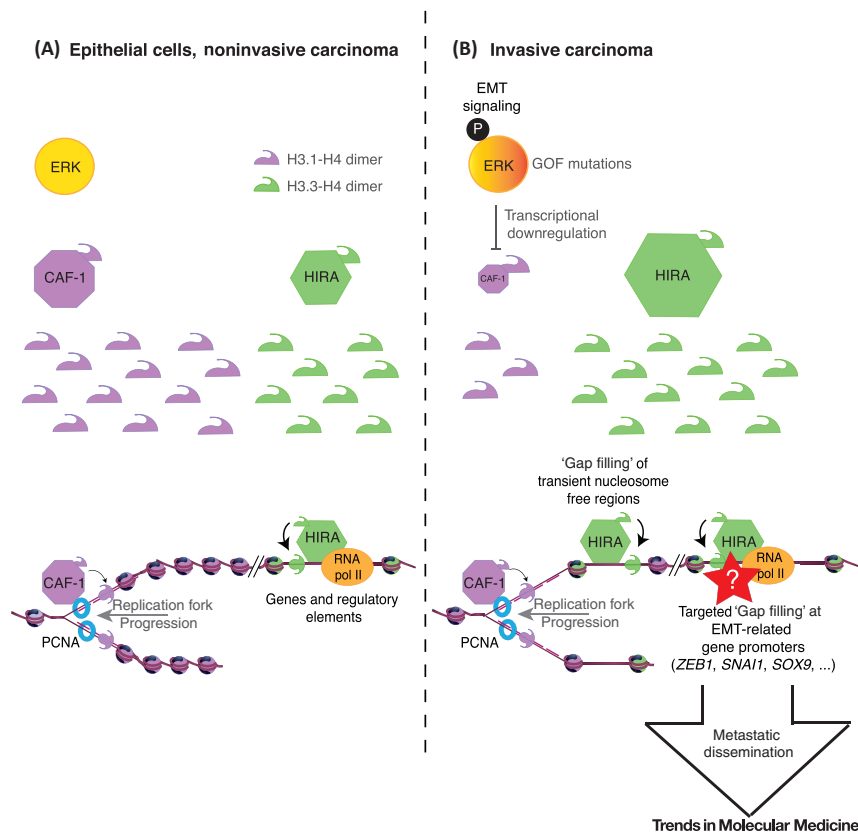
ensures the deposition of H3.3 throughout the cell cycle at actively transcribed regions, while the ATRX/DAXX complex is rather involved in H3.3 enrichment in heterochromatin regions at telomeres and peri-centromeres. However, when H3.1 incorporation is compromised at DNA replication sites, HIRA-dependent H3.3 deposition kicks in. This alternative H3.3 deposition at places of histone loss has been proposed to act as a 'gap-filling' mechanism to prevent nucleosome-free DNA accumulation and preserve chromatin stability [4].

Histone H3 variants play essential roles during development, cell fate determination, and cellular reprogramming [3], and mutations thereof have been identified as oncohistones [5]. Epithelial mesenchymal transition (EMT), which promotes cell motility and differentiation as well as resistance to apoptotic stimuli during early development, is frequently co-opted by cancer cells to promote metastatic formation and dissemination [1,2]. Gomes and colleagues addressed how histone H3 variant dynamics are involved in cell reprogramming during metastatic transition [2]. In a variety of epithelial or carcinoma cell lines, after EMT and metastasis induction by using TGF- $\beta$ /TNF $\alpha$  or expression of mutant form of ERK, they observe increased chromatin accessibility and a general decrease of total histones incorporated into chromatin. This general loss of histones is reflected at the mRNA and protein levels for histone H3.1. However, in sharp contrast, under the same conditions, H3.3 incorporation into chromatin increased (Figure 1). This finding is reminiscent of the histone loss that facilitates reprogramming and 'gap-filling' by H3.3 [4]. Remarkably, instead of a random H3.3 enrichment, the authors find enrichment of H3.3 at specific promoters corresponding to genes involved in EMT, such as *ZEB1*, *SNAI1*,

and *SOX9*, all associated with induction of protumoral transcriptional programs, including tumor progression, metastasis, and wound healing (Figure 1).

Given the roles of CAF-1 and HIRA in escorting histone H3 variants for their incorporation into chromatin, the authors analyzed the levels of these histone chaperones. While CAF-1 decreased, HIRA proteins increased in response to EMT and metastasis inducers. Further analyses show that the decrease of CAF-1 levels is due to downregulation of its subunit CHAF1B mRNA expression, ultimately resulting in destabilization of the whole CAF-1 complex. This is achieved through inhibition of phosphorylation of a key CHAF1B transcriptional regulator, Sp1. In a series of gain- and loss-of-function experiments, the authors finely dissected the implication and importance of CAF-1, HIRA, and H3.3 in this metastatic reprogramming. They found that reduction of CAF-1 is sufficient to induce EMT-related gene expression in a variety of cancer cell lines and thereby confers resistance to anticancer drugs, such as paclitaxel and carboplatin. In an animal xenograft model, they further document increased tumor growth under similar conditions. Finally, the ectopic CAF-1 overexpression in an aggressive breast metastatic cell line LM2 prevented tumor growth, demonstrating that this axis represents a valuable means for therapeutic intervention. In contrast, the ectopic overexpression of H3.3, HIRA, or DAXX did not result in the acquisition of metastatic signature, namely fibronectin expression and loss of E-cadherin. Yet, reduction of either H3.3 or HIRA levels in LM2 cells by shRNA was sufficient to lose fibronectin and induce E-cadherin expression, indicating a loss of metastatic properties. Intriguingly, *H3F3A* overexpression, one of the two genes encoding H3.3, has been previously involved in promoting lung cancer cell invasion and associated with relapse and poor prognosis





**Figure 1. Histone H3 Chaperone-Dependent Chromatin Reprogramming Promotes Carcinoma Invasiveness**

(A) In epithelial cells and noninvasive carcinoma, the ERK signaling pathway is not activated by oncogenic signals. The histone H3.1 (purple) is incorporated into chromatin by the chaperone CAF-1 during DNA replication, while the histone H3.3 variant (green) is incorporated at genes and regulatory elements by its chaperone HIRA. HIRA is also proposed to incorporate H3.3 at transient nucleosome free regions by 'gap filling', not represented here. A balance between the levels of H3.1 and H3.3 and their chaperones maintains the nucleosomal density at the chromatin level. (B) In invasive carcinoma, gain-of-function mutations of ERK or oncogenic stimuli leading to ERK activating phosphorylation (black circle), trigger a transcriptional downregulation of CAF-1. This is accompanied by a dramatic decrease in the histone H3.1, an increase in H3.3 levels (although total histone H3 levels remain reduced), and an increase of HIRA levels. The depletion of CAF-1 results in a reduction of H3.1 variant incorporated into chromatin. Gomes *et al.* propose a model where the arising 'naked DNA gaps' are subsequently filled in by H3.3 in a HIRA-dependent manner. HIRA and probably other unknown factors (red star) target H3.3-specific enrichment at promoters of EMT inducers such as *ZEB1*, *SNAI1*, and *SOX9* and favors their expression. This promotes in turn a cellular transcriptional reprogramming toward a more aggressive metastatic colonization. Abbreviations: CAF-1, chromatin assembly factor 1; EMT, epithelial to mesenchymal transition; ERK, extracellular signal regulated kinase; GOF, gain-of-function; PCNA, proliferating cell nuclear antigen; Sox9, sry-related high mobility group box 9; ZEB1, zinc-finger E-box binding homolog 1.

[6]. Histone H3.3 enrichment at intronic DNA regulatory elements proved critical to activate the G protein-coupled receptor 87 (GPR87), acting upstream of ERK signaling [7].

In summary, the results of Gomes and colleagues stress how ERK signaling leads to both downregulation of CAF-1 and a decrease in nucleosome density, thereby enabling cell repro-

gramming leading to resistance to anti-cancer therapies. This is accompanied by HIRA-dependent H3.3 incorporation at the promoters of transcription factors involved in the induction of EMT, which fuels metastatic progression. Given that HIRA reduction reverts the metastatic properties of LM2 cells, the authors put forward HIRA as a promising therapeutic target. The reduced levels of CAF-1 in metastatic breast carcinoma, when compared with their matched primary tumors, supports the findings of Gomes *et al.*

Previous studies have implicated CAF-1 as a barrier to embryonic stem cell reprogramming, at least in part by regulating chromatin accessibility [8]. The findings of Gomes *et al.* imply that a similar mechanism likely occurs in tumor cells during the transition toward metastatic progression. While the H3.3 gap-filling deposition is thought to occur without DNA sequence specificity through recognition of naked DNA by HIRA, in the study by Gomes *et al.*, HIRA brings H3.3 to specific promoters. Understanding how this specific H3.3 deposition is controlled will be exciting. Furthermore, HIRA functions as a complex and with partners, and the recent characterization of its trimerization properties offers interesting avenues to explore how this specificity could be achieved [9]. Fully understanding the role of histone H3 variant dynamics during metastasis will be a major future challenge, relevant not only for cancer but also for other physiological cellular reprogramming events associated with development and/or disease transition. In particular, deciphering the underlying molecular processes that control H3.3 and HIRA upregulation upon metastatic induction will be an important step to find means to prevent metastasis.

Given that such changes can affect subpopulations of cells in a tumor, new

approaches such as fluorouracil-labeled nascent RNA sequencing, designed to detect rare cell populations' trajectories *in vivo* and *in situ* [10] and single cell technologies will be instrumental to appreciate tumor heterogeneity and the transcriptional changes upon metastatic reprogramming and, ultimately, to resolve the challenges imposed by metastatic divergent clonal evolution [11].

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### Spotlight

## Boosting Antitumour Immunity through Targeted Delivery of Interferon- $\alpha$

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Immune checkpoint inhibitors (ICIs) have revolutionised cancer immunotherapy but their success is wholly dependent on amplifying an existing immune response directed against the tumour. A recent study by Tsuchiya *et al.* suggests how the properties of induced pluripotent stem cells (iPSCs) may be exploited for the targeted delivery of interferon- $\alpha$  (IFN $\alpha$ ) to elicit an appropriate response.

Recent years have witnessed the renaissance of tumour immunology, driven, in part, by the advent of ICIs, monoclonal antibodies specific for inhibitory receptors such as programmed death-ligand 1 (PD-L1) expressed within the tumour microenvironment, the blockade of which releases the brakes on immune responses, maximising their antitumour activity. Success is, however, predicated on the existence of an ongoing immune response to the tumour, which is itself dependent on high genomic

instability, responsible for the generation of suitable neoantigens: those tumours that fail to elicit an effective immune response, so-called 'cold' tumours with a low mutational burden, are largely refractory to immune intervention [1]. However, it is not merely amplification of existing immune responses that ICIs seek to achieve but rather their vigorous initiation by dendritic cells (DCs): by altering the balance of stimulatory and inhibitory signals delivered to naïve T cells, the likelihood of initiating an immune response of appropriate magnitude is greatly increased.

But not all DCs are equally effective at eliciting antitumour immunity since the capacity to acquire exogenous tumour-associated antigens (TAAs) and present them via MHC class I, a process known as antigen cross-presentation [2], is a prerequisite for activation of CD8<sup>+</sup> cytotoxic T lymphocytes (CTLs). This property is confined to rare subsets of DCs that collectively express the chemokine receptor XCR1 [3], responsible for guiding them within the tumour-draining lymph nodes (dLNs) towards CD8<sup>+</sup> T cells that secrete the ligand, XCL1. XCR1<sup>+</sup> DCs are surprisingly rare, especially within the tumour itself, which they are known to actively infiltrate. Furthermore, they must undergo maturation before they are able to migrate to the dLNs and elicit a response to TAAs acquired *in situ* [4]. This process is normally dependent on the sensing of cytosolic DNA via the so-called stimulator of IFN genes (STING) pathway, or the local secretion of potent proinflammatory cytokines, such as IFN $\alpha$ , neither of which is abundant in the sterile microenvironment of a solid tumour, representing a significant weak link in antitumour immunity.

Various groups have sought to plug this gap by exploiting the unique properties

