The histone H2A isoform Hist2h2ac is a novel regulator of proliferation and epithelial--mesenchymal transition in mammary epithelial and in breast cancer cells

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Genetic programs determine cell function. Understanding how accessibility to genetic information occurs in the normal functional differentiation process helps us understand the deregulations observed in diseases such as cancer. Genetic information is encoded in our DNA, which is packaged and compacted into the cell´s nucleus. Histones are a class of proteins used to package the DNA; the level of packaging is regulated by multiple chemical modifications in these proteins and determines whether the genetic information contained in our genes can be accessed by the cell. There are four canonical histone families H2A, H2B, H3, and each one of these families comprises several isoforms. Until recently, canonical histone isoforms were assumed to be functionally redundant and intercheangeable within each class. This is mainly due to their high degree of homology which does not allow straight forward analysis.

AIM: In this study, we aimed to identify changes in the canonical histone profiles throughout the normal cell differentiation process and correlate findings with alterations observed in breast cancer.

RESULTS: Using a combined mass spectrometry and transcriptomics approach, we were able to identify over 23 histones differentially expressed in highly proliferating/poorly differentiated cells as compared to functionally differentiated cells. Among these proteins, Histone H2A type 2-C (Hist2h2ac) was particularly high in undifferentiated cells with high division rate (highly proliferative) cells. Poor differentiation and high proliferation are characteristics of cancer cells and we found that Hist2h2ac is necessary for the cells to keep their undifferentiated phenotype (by decreasing the cell adhesion protein E-cadherin and increasing the oncogenic protein Zeb-1). We also established that high Hist2h2ac levels are maintained by stimulation of MAPK/ERK and PI3K/AKT intracelular pathways, which are activated by epidermal growth factor (EGF). EGF plays an important role in cancer, through stimulation of proliferation and we observed that by inhibiting Hist2h2ac expression, breast cancer cells could not proliferate when stimulated by EGF. Finally, we also studied Hist2h2ac expression in human breast cancer samples and observed that it is mutated or upregulated in about 16% breast cancers analysed.

CONCLUSION: Cannonical histone isoforms are specifically regulated according to the differentiation stage of the cells. Therefore, they are not interchangeable. Moreover, we propose that Hist2h2ac is signalling hub which is kept in high levels by EGF and at the same time is needed to allow the cells to respond to this growth factor and proliferate. In the future, we plan to study in more detail the genetic programs regulated by Hist2h2ac in human breast cancer so we can determine if blocking its expression can inhibit tumour growth.

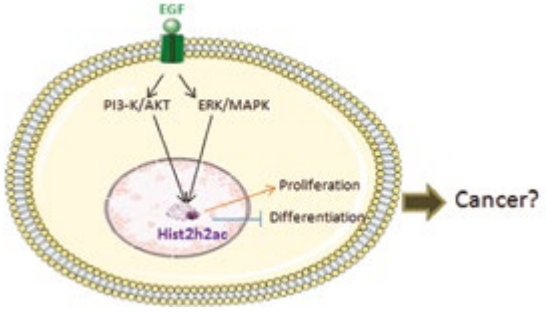

FIGURE 1
Schematic representation of main findings from the study.

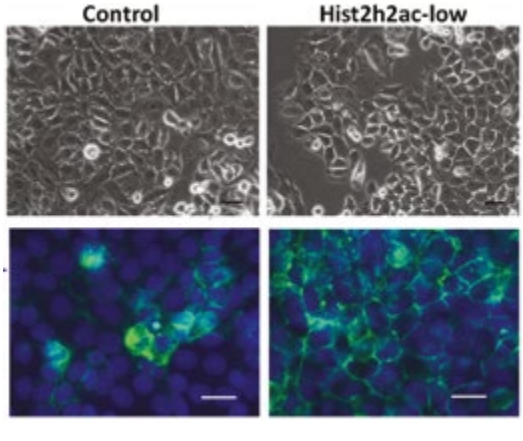

FIGURE 2
Hist2h2a inhibition (Hist2h2a-low cells) results in enhanced cell differentiation correlating to higher E-cadherin levels (green). Blue: nuclei.