CNIO - LILLY EPIGENETICS SECTION

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"Our goal is to identify epigenetic events that contribute to tumourigenesis and that might be susceptible to modulation by therapeutic agents."

SCOPE OF THE CNIO - ELI LILLY PARTNERSHIP

Eli Lilly and CNIO are collaborating on the identification and validation of novel targets in cancer epigenetics. Our Section is funded through a research contract with Eli Lilly and focuses on the identification of small molecular weight molecules that are able to modulate the epigenome of malignant cells, and ultimately block the growth and spread of tumours. Potential targets (FIGURE) are being validated *in vitro* and *in vivo* using animal models developed at the CNIO. Furthermore, we are currently setting up biochemical and cell-based assays with the aim of understanding the mechanism of action of such targets at the molecular level.

SCIENTIFIC CONTEXT

Recent studies have shown that the alterations that take place in cancer cells not only occur at the DNA sequence but also at the level of the epigenome. Eukaryotic DNA is wrapped around histone proteins to constitute chromatin, which plays fundamental structural and regulatory roles. The epigenome consists of chemical changes in both DNA and histones that can be inherited through cell division and are controlled by the action of a large set of epigenetic regulators that possess enzymatic activity. Ultimately, DNA and histone modifications control the level of chromatin condensation, which in turn regulates the accessibility of transcription factors to the chromatin and, therefore, gene expression.

During the past few years several studies, including our own, have suggested that the deregulation of the chromatin-modifying machineries can lead to aberrant gene expression causing cancer and other human diseases. The epigenome is regulated in a highly dynamic fashion by the coordinated action of regulators that are able to write, erase and read histone and DNA modifications (FIGURE). Thus, contrary to genetic mutations, epigenetic aberrations can be reversed by targeting the appropriate epigenetic regulators. Indeed, drugs targeting DNA methyltransferases and histone deacetylases have successfully demonstrated anticancer properties and are currently used in the clinic. Therefore, identifying the molecular function of critical epigenetic regulators and their complex relationship with the cancer epigenome, as well as the development of small molecular inhibitors of their activities, hold great promise for cancer therapy (FIGURE). ■

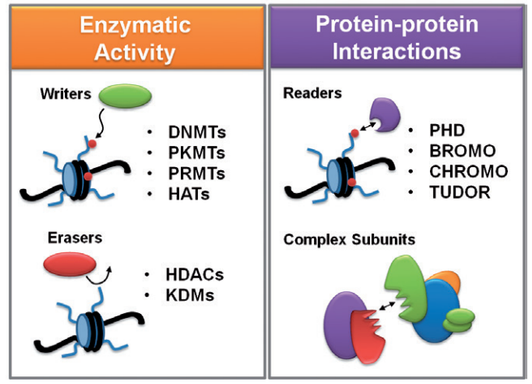

Figure Strategies for targeting epigenetic regulators. The enzymatic activities of DNA methyltransferases (DNMTs), protein lysine methyltransferases (PKMTs), protein arginine methyltransferases (PRMTs), histone acetyltransferases (HATs), histone deacetylases (HDACs), or lysine demethylases (KDMs), are amenable to inhibition by small molecules. Additionally, molecular probes can be used to block the interactions of readers containing PHD, Bromo, Chromo or Tudor domains with modified histones, or to disrupt the interaction between critical core components of chromatin-related complexes.

PUBLICATIONS

- García-Carpizo V, Sarmentero J, Han B, Graña O, Ruiz-Llorente S, Pisano DG, Serrano M, Brooks HB, Campbell RM, Barrero MJ (2016). NSD2 contributes to oncogenic RAS-driven transcription in lung cancer cells through long-range epigenetic activation. *Sci Rep* 6, 32952.
- Castaño J, Morera C, Sesé B, Boue S, Bonet-Costa C, Martí M, Roque A, Jordan A, Barrero MJ (2016). SETD7 Regulates the Differentiation of Human Embryonic Stem Cells. *PLoS One* 11, e0149502.