

Chromatin associated PI(4)P regulates lysine-specific histone demethylase 1

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Phosphoinositides are glycerol-based phospholipids. They are composed of hydrophobic fatty acid tail and hydrophilic inositol head. Phosphoinositides are important cytoplasmic signalling molecules. They participate in various processes such as modulation of ion channels and transporters, membrane dynamics and cellular movement. Despite the absence of membranes inside of the nucleus, phosphoinositides are implicated in essential nuclear processes. Through the interaction with their binding partners, they regulate DNA damage response, RNA processing and they regulate DNA transcription by interacting with RNA polymerases and transcription factors or by regulation of chromatin remodelling and modifications. Phosphatidylinositol 4-phosphate [PI(4)P] is one of the most abundant phosphoinositides in the cell, however, its nuclear functions are still poorly understood. Our preliminary data show that PI(4)P localizes to the nuclear membrane, nuclear speckles and forms small foci in the nucleoplasm. The majority of PI(4)P is associated with active chromatin. Lysine-specific histone demethylase 1 (LSD1), which demethylates H3K4me2 and H3K4me1, binds with the highest affinity to PI(4)P and binds also PI(3,4)P2, PI(3,5)P2, PI(4,5)P2 and PI(3,4,5)P3. While in a complex with PI(4)P, the activity of LSD1 is inhibited. On the other hand, the interaction with PI(4,5)P2 stimulates LSD1 demethylase activity *in vitro*. Since PI(4,5)P2 is a precursor/product of PI(4)P (de)phosphorylation, a single change in phosphorylation of inositol ring could provide a rapid regulation of LSD1 function also *in vivo*.

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