ABSTRACT (ENGLISH)

Phosphoinositides (PIs) are negatively charged glycerol-based phospholipids. Their inositol head can be phosphorylated at three positions generating seven differently phosphorylated species. Cytoplasmic phosphoinositides regulate membrane and cytoskeletal dynamics, vesicular trafficking, ion channels and transporters and generate second messengers. In the nucleus, PIs are implicated in pre-mRNA processing, DNA transcription and chromatin remodelling. However, their nuclear functions are still poorly understood. Here we focus on nuclear phosphatidylinositol 4-phosphate (PI(4)P) and phosphatidylinositol 4,5-bisphosphate (PI(4,5)P2). We describe their localization and interaction with proteins involved in regulation of DNA transcription.

PI(4)P localizes to nuclear membrane, nuclear speckles and nucleoplasm. The majority of nuclear PI(4)P is associated with chromatin and colocalizes with H3K4me2. PI(4,5)P2 localizes to nucleoli and nuclear speckles. Besides, 30 % of nuclear PI(4,5)P2 forms small nucleoplasmic PI(4,5)P2 islets. They have carbon rich core, which is probably formed by lipids, and are surrounded by proteins and nucleic acids. The active form of RNA polymerase II associates with PI(4,5)P2 islets and DNA is actively transcribed in the vicinity of PI(4,5)P2 islets. Moreover, nuclear myosin 1 (NM1) binds PI(4,5)P2 in the nucleus. This interaction targets NM1 to PI(4,5)P2 islets and is essential for NM1 interaction with transcription machinery and active DNA transcription. Therefore, we suggest that PI(4,5)P2 islets facilitate spatial-temporal arrangement of transcription complexes assembly.

Moreover, we demonstrate that lysine-specific histone demethylase 1 (LSD1), enzyme that demethylates H3K4me2, interacts with both PI(4)P and PI(4,5)P2. While the interaction with PI(4)P leads to inhibition of LSD1, the interaction with PI(4,5)P2 stimulates LSD1 H3K4me2 demethylase activity *in vitro*. Thus, PI(4)P and PI(4,5)P2 could regulate transcription at the epigenetic level also *in vivo*.

Another PI(4,5)P2 binding protein, actin, exists in the cytoplasm in monomeric form that can polymerize to filaments. However, in which form is actin present in the nucleus is still not sufficiently understood. After actin overexpression, we observed formation of actin filaments in the nucleus. These filaments resemble cytoplasmic F-actin and recruit cofilin and Arp3 actin binding proteins. Formation of actin filaments in the nucleus results in increased transcription in S-phase, decreased cell proliferation and aberrant mitosis.