Intracellular aggregations of biological elements: From simple to complex

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Abstract
Most cellular elements could be functioned by forming aggregate structures through interactions with other molecules, which is like the luminescence mechanism of AIE molecules. However, in comparison to AIE molecules, the aggregation of biological elements appears to be more complex due to membership and mechanism, which is in line with the trend in biological evolution following the principle of simplicity to complexity. Here, we chose three distinctive examples because they differ significantly in their composition and show a progression from simple to complex, namely protein–protein complexes, protein–nucleic acid complexes, and protein–nucleic acid–lipid complexes. The majority of units that perform functions within cells belong to these three types. We discuss the formation mechanisms and related functions of the protein–protein complex (PML-NB), the proteins–nucleic acids complex ribosome, and the proteins–nucleic acids–lipids complex exosome, and hope to provide expert insight for related fields.

KEYWORDS exosome, PML nuclear body, PML-NBs, ribosome

INTRODUCTION
Organic luminescent materials have been the focus of many studies and shown to be emerged as important tools for diagnosis and treatment of diseases due to the materials containing flexibility of design and predictability of functions.[1] Theranostics utilizing fluorescence molecules for imaging allows precise diagnosis and subsequent personalized treatment.[2] However, traditional fluorescent chromophores will weaken or even not emit light at high concentrations, which is called the “concentration quenching” effect. The main reason for concentration quenching is the formation of aggregates, so the phenomenon is usually called “aggregation-caused quenching (ACQ)”. Despite researchers have tried to reduce ACQ effect through various chemical, physical, or engineering methods, the effects were limited.[2,3] Application of fluorescence molecules with “aggregation-induced emission (AIE)” characteristic could partially overcome this challenge. In 2001, the research group of Professor Tang Ben Zhong identified a peculiar phenomenon that some silole molecules hardly emit light in solution, while their luminescence was greatly enhanced in the aggregate state or in a solid film, which was defined as aggregation-induced emission.[3,4] One of the great features of AIEgens is enhanced fluorescence due to aggregation of AIEgens, which is similar to the
mode of operation of most biological elements, that is, there is strength in numbers. Cells consisted of a wide variety of biological elements, such as nucleic acids, proteins, and lipids. Although some of these function as monomers, most of them tend to perform their functions through complex interactions. In order to better understand the biological activities of cells, it is important to clearly understand the formation of complexes and the mode of action. Biological evolution has been accompanied by the evolution of biological units from simple to complex, implying an increasing complexity of functional executive units. In this context, synergistic interactions of proteins, liposomes, nucleic acids, etc., play an important role.

The study of the complexes formed by various biological elements for functioning can not only reveal the functions of the components but also provide an important foundation for suggesting the rules of cell activities such as growth, development or apoptosis, as well pave ways for exploring the mechanisms of major diseases, disease treatment, disease prevention, and new drug development. This article introduces the formation and functions of three important complexes in cells, namely, PML nuclear bodies (PML-NBs) (protein complex), ribosomes (protein–ribonucleic acid complex), and exosomes (nucleic acid–protein–lipid complex), which are chosen due to their distinctive function and the progression from simple to complex, and aims to provide insight into the study of the cellular aggregation of biological elements.

PML NBs: Structure, formation, and function

PML-NBs, which were previously known as PML oncogenic domains, nuclear domains-10, and kremen,[5] are dynamic multiprotein complexes existing in the nuclear matrix with highly ordered aggregation based on PML polymer skeleton, which is constructed by PML dimers formed through the coiled-coil region (CC region). These structures are composed of PML proteins multimer storing a series of transiently associated client proteins, and devoid of clearly defined nucleic acids.[6] (Figure 1). The diameter of PML-NBs is approximately 0.2–1.0 μm. Electron microscopy studies reveal that PML-NBs are discrete nuclear foci being present in most mammalian cell nuclei and generally 1–30 bodies per cell. These discrete aggregations appear as spherical subcellular structures implicated in a broad range of cellular processes ranging from senescence to viral infections or stemness, since over 100 partner proteins were serendipitously identified, and their NB location altered following cell or environment stress.[6–8]

The PML tumor suppressor gene, also called MYL, RNF71, PP8675 or TRIM19, was first cloned in 1991, which encodes the tumor suppressor protein PML, belonging to TRIM subfamily of which the members share a conserved N-terminal structure containing one RING domain, one or two zinc-finger domains named B-box(es) (B1 box or B2 box), and a coiled-coil region.[9,10] A large number of alternatively spliced PML transcripts generate a variety of PML isoforms that have an iconic N-terminal area and differ in their C-terminal sequence.[11] N-terminal of PML mediates the homomultimerization, while the different of C-terminal determine the interactions of PML with the client proteins. Different subtypes of PML construct PML-NBs through the coiled-coil regions, but different forms of PML-NBs are observed in PML–/– cells transfected with single subtype of PML, demonstrating that the C-terminals of PML determine structure of PML-NBs.[12]

The fact that expression of PML-RAR fusion protein resulting from a t(15;17) chromosomal translocation predisposes patients to acute promyelocytic leukemia (APL) attracts attentions of scientists.[13] The translocation between PML gene on chromosome and RAR gene on chromosome 17 produces PML-RAR fusion gene. The t(15;17) translocation, where RAR gene is broken at upstream of exon 4, and PML gene is broken in intron 3, exon 6 or intron 6, forms three types of PML-RAR fusion genes, PML-RAR long (PML-RARL), PML-RAR short (PML-RARγS), and PML-RARγV, of which PML-RARL is expressed in approximately 55% of adult APL patients, while PML-RARγS and PML-RARγV are expressed in approximately 35% and 8% of patients, respectively.[14–17] PML-RAR fusion protein has many key domains of PML, since the broken sites of PML gene locate in intron 3, exon 6 or

![FIGURE 1 Formation and location of PML-NBs](image-url)
introns, and the RING finger and the B1 and B2 boxes are mainly encoded by exons 2 and 3, and the coiled-coil region is mainly encoded by exon 3.\textsuperscript{14} PML-RAR\textsubscript{α} fusion proteins can form a heterodimer with wild-type PML proteins through the coiled-coil region leading to dissociation of PML from PML-NBs and disability to bind related partner proteins. Meanwhile, PML-RAR\textsubscript{α} fusion proteins lose functions of PML due to their lack of C-terminus of PML. Yet, the loss of nuclear localization signal located in the proximal region of PML exon 6 in PML-RAR\textsubscript{α} limits its role in disturbing PML-NBs formation. Despite RAR\textsubscript{α} is critical for the differentiation of bone marrow hematopoietic stem cells, overexpression of PML-RAR\textsubscript{α} fusion protein instead of RAR\textsubscript{α} mutation induces APL, which displays diffusion of PML-NBs.\textsuperscript{15,18–20}

Over the past decades of years, scientists make big efforts to understand the cellular functions of PML-NBs through primarily focusing on the identification of proteins that localize at PML-NBs. In spite of the purification of the PML partner proteins has proven elusive, many clients have been identified to locate to PML-NBs as structural members or temporary existence through these efforts. Consequently, PML-NBs have been involved in multiple cellular processes including transcriptional regulation, viral infection response, DNA damage response, cell proliferation, cell senescence, and apoptosis.\textsuperscript{9,13,21–23} Approximately a hundred client proteins are found at PML-NBs, many of which are constitutive, but most of the proteins are dynamically changing in response to environmental stresses, whereby PML-NBs regulates various cell functions. Disruption of PML-NBs results in aberration of cellular pathways resulting in diseases such as APL. One of the most clearly defined and focused functions of PML NB is the regulation loops between p53 and PML NB, whereby PML NB opposes cell transformation and acts as a tumor suppressor. PML-NBs recruit p53 and the modifying enzymes, which maintain p53 stabilization and potentiate p53 function, such as CBP-dependent acetylation and Chk2-dependent phosphorylation. Particularly, PML-NBs stabilize p53 by sequestering MDM2 protein and limiting its function. For APL treatment, PML-RAR\textsubscript{α} fusion protein degradation induced PML-NBs reconstruction activates p53-mediated cell senescence.\textsuperscript{124} In cellular ROS-responsive study, PML significantly regulates p53 signaling pathways.\textsuperscript{25} The fact that PML act as a bona fide transcriptional target of p53 potentiates its tumor suppressor effects, displaying a positive feedback loop.\textsuperscript{22,26}

Ribosomes are aggregate structures of RNA and proteins with a diameter of 25–30 nm. The ribosome of human is also called 80S ribosome since it has a sedimentation coefficient of 80S. 80S ribosome is composed of two subunits, a 60S subunit and a 40S subunit, and contains four kinds of rRNA and approximately 80 different ribosome proteins (RPs). The 60S subunit consists of 5S rRNA, 28S rRNA, 5.8S rRNA, and 46 RPs, while the 40S subunit contains 18S rRNA and 33 distinct RPs. The ribosomal proteins that make up the large and small subunits are defined as the ribosomal protein large subunit (RPL) and the ribosomal protein small subunit, respectively.

As a large complex of rRNA and RPs, ribosome is mainly synthesized in nucleolus. The enlargement of nucleolus often reflects increased synthesis of ribosome. Electron microscopy shows that the nucleolus contains three main structures: fibrillar center (FC), dense fibrillar component (DFC) and granular component. Ribosome DNA (rDNA) is located and transcribed in the FC, and the rRNA newly synthesized from rDNA are mainly concentrated in the DFC. The DFC is important for rRNA processing. The granular component provides a place for further processes and construction.\textsuperscript{221} The FC contains all the substances required for the rDNA transcription process, including Pol I, upstream binding factor (UBF), nucleolin and nucleolar phosphate protein, and so on, which can be colored by silver staining.

Approximately 400 copies of rDNA genes are divided into active state, silent state, and poised state according to the characteristics of epigenetic modification and transcription activity.\textsuperscript{22,29} ratios of which are changed between different differentiated states of cells. With the assistance of PolII and at least three important factors, Rrn3 (TIF-IA), SL1/TIF-IB (selectivity factor 1, SL1), and UBF, active rDNA is transcribed to 47S pre-rRNA, which is then processed into mature 18S, 5.8S, and 28S rRNA. Another rRNA, 5S rRNA, is synthesized by RNA polymerase III in nucleoplasm and then transported to nucleolus. Messenger RNAs (mRNAs) of RPs are transcribed by RNA polymerase II, and then translated into mature proteins in cytoplasm, which are transported to nucleolus subsequently. Then, 28S, 5.8S, 5S rRNA, and 49 kinds of RPs are assembled into 60S subunit, while 18S and 33 kinds of RPs are assembled into 40S subunit, and finally, the large and small subunits are transported to cytoplasm to form 80S ribosome (Figure 2). Throughout the process, rDNA transcription is the limiting step during ribosome biosynthesis.

Ribosomes are responsible for translating the genetic code and synthesizing protein. Its main function is to take advantage of the mutual recognition of mRNA and rRNA to translate nucleotide sequence into polypeptide chain. Ribosomes have been considered as a static entity in the past, but in recent years, accumulated studies reveal that ribosomes are heterogeneity and highly regulated. Mechanisms leading to ribosomal heterogeneity are manifold. Changes of RPs expression and modification of rRNAs and RPs emerge to adapt to environmental changes.\textsuperscript{30–32} Some of proto-oncogenes and tumor suppressors have been shown to regulate ribosome biosynthesis or initiation of protein translation, such as phosphatidylinositol 3-hydroxy kinase (PI3K), MYC, mTOR, p53, and RB.\textsuperscript{30,31,33} Moreover, abnormal expression of RPs often occurs in tumors, such as the overexpression of RPL7A, RPL19, and RPL37 in prostate cancer.\textsuperscript{34,35} and the low expression of RPL27, RPL37A, and RPL41 in nasopharyngeal carcinoma.\textsuperscript{36} Ribosomal heterogeneity of tumor cells is particularly prominent and may be related to tumor progression, which may shed light into oncotherapy.

Exosomes: Structure, formation, and function

Exosomes are lipid bilayer membrane vesicles secreted by almost all types of cells with a diameter of 30–150 nm and a density of 1.11–1.19 g/mL varying with the donor cell and
proteins content. The surface of exosomes is rich in lipids such as cholesterol, sphingomyelin, and ceramide, and the inside contains lots of signaling or functional substances such as proteins and microRNAs, playing critical roles in intracellular signaling.[37-39] Exosomes were first identified in sheep reticulocytes in 1983,[40,41] and further termed “exosome” by Johnstone et al. in 1987.[42] Exosomes are initially considered experimental artifacts, waste products, or residues of dead cells,[40] until they are likely to be a new way for intercellular communication by Zitvogel et al. and Raposo et al. in the 1990s.[43,44] In 2007, Valadi et al. found that exosomes containing nucleic acids (mRNA, microRNA, etc.) and proteins can be captured by the other cells.[45] A transmission electron microscope image reveals that exosomes are mostly saucer-shaped or a hemispherical with concave on one side.

Many mechanisms reported exosomes formation,[46] the classic way is endosomal sorting complexes required for transport (ESCRT) dependent. More than 20 vesicles sorting proteins are involved in the formation of multivesicular body (MVB). Four ESCRT complexes, including ESCRT-0, ESCRT-1, ESCRT-2, and ESCRT-3, and various auxiliary proteins, such as Alix, Vps4, and VTA-1, jointly participated in the formation of MVB. ESCRT functions for membrane remodeling resulting in endosomes budding and MVBs formation, wherein ubiquitinated proteins are sorted.[47,48] At the beginning of the ESCRT-dependent pathway, ESCRT-0 bind and clustering ubiquitinated proteins on endosomal membrane to form microdomains by means of an HRS heterodimer and STAM1/2.[49-51] Next, ESCRT-1 and ESCRT-II join the ESCRT-III and are response to inducing endosomal budding and protein sorting. Finally, ESCRT-III shrinks and shears the bud to help buds to release into the endosome.[52] ESCRT-III is considered as the most important member of ESCRT machinery since it plays a role in all ESCRT-dependent processes.[53] AAA-type (chaperone-like) ATPase Vps4 is then required to dissociate ESCRT complexes from membrane allowing them for recycle (Figure 3).[54,55] Various substances are sorted into exosomes benefitting from budding inward. There are conserved constitutive proteins present on the membrane of exosomes, such as CD9, CD63, CD81, and so on; even the exosomes are secreted by different types of cells. In the meanwhile, specific compositions could be a characterization for the donor cells identification.[56] more importantly, the different compositions of exosomes can also reflect the physiological or pathological changes.[57] The secretion of exosomes once formed relies on the interaction and fusion between exosomes and the internal side of the plasma membrane, wherein SNARE complex (soluble N-ethylmaleimide-sensitive fusion attachment protein receptor) plays an important role.[58] The formation and secretion of exosomes are continuous processes, which can be affected by environmental stresses, such as reactive oxygen species, UV radiation, cholesterol decrease, and calcium ion increase.

To some extent, exosomes are aggregates of lipids, proteins, and nucleic acids, variety of which is cell type specific and response to environmental stresses. Lipids are essential components of exosome membranes, and hundreds of lipids have been identified. Similar to the parent cells, exosomes are rich in sphingomyelin, ganglioside, and unsaturated lipid;[59] moreover, phosphatidylserine of exosome may help exosomes to be easily recognized and endocytosed by recipient cells.[60] In the meanwhile, the lipids of exosomes can also be used as signal to participate in biological processes. For example, the lipids of exosomes secreted by pancreatic cancer cells have been confirmed to promote cancer cell apoptosis through the Notch pathway.[61] Various proteins are present in exosomes, including conservative members and specific members differing with donor and environment. Additionally, exosomes are rich in glycoproteins and transmembrane proteins, which facilitate their recognition and uptake by recipient cells.[62] Except for lipids and proteins, abundant nucleic acids exist in exosomes, including mRNA, microRNA, circular RNA, long noncoding RNA, and DNA, which play important roles in intercellular signaling.

**DISCUSSION**

Abnormal intracellular aggregation often leads to dysfunction of cell processes, which is similar to the ACQ effects wherein fluorescent chromophores quench at high concentrations. In the meanwhile, the formation of the complexes we focus on in this paper are critical for the execution of their functions,
which is like AIEgens. Various complexes are the basic units of cellular activities, and the investigation of the formation mechanism of complexes and the provision of corresponding protection are of great significance.

PML-NBs are unique aggregates of nuclear-localized proteins that are involved in the regulation of a wide variety of cellular processes by regulating the immobilization, release, and posttranslational modification of the participating members. As functionally significant genes, cellular PML levels were regulated at the RNA and protein levels, which demonstrate the crucial role of PML levels for PML-NBs formation; furthermore, SUMOylation of PML is considered essential for the synthesis of PML-NBs. PML-NBs undergo significant changes in number, size, and location in response to specific cellular stress states. Many proteins are found partially, temporarily, or as constitutive components localized to PML-NBs, and the complexity of PML-NBs suggests that they are involved in the regulation of almost every biological activity. In the meanwhile, a wide variety of natural proteins accumulate on PML-NBs, making it difficult for these structures to exhibit a proprietary or distinct biochemical function. In addition to functioning as a repository for protein aggregation by regulating the localization of associated proteins and by isolating or mediating protein interactions, PML-NBs may also function as a catalytic unit by catalyzing posttranslational modifications of aggregated proteins, since most hypotheses suggest that PML may function as a SUMO E3 enzyme due to the presence of the RING domain. It is also noteworthy that because environmental stresses can trigger changes in PML-NB localization, PML-NBs may serve as anchor sites that mediate biological processes in the nucleus. It calls for research on members of PML-NBs, their aggregation mechanisms, and related functions for the prevention and treatment of specific diseases by regulating PML-NBs-dependent protein aggregation and corresponding functions. The study on the effect of arsenic trioxide on the formation of PML-NBs by inhibiting PML-RARα and thus promoting the formation of natural PML-NBs and the treatment of APL provides a good case for this proposition.

The ribosome is one of the most important organelles in the cell and is responsible for the process of translating the genetic information contained in DNA into protein. Briefly, RNA polymerase II uses DNA as a template to synthesize mRNA (transcription) and ribosomes are guided by the mRNA to synthesize the corresponding proteins (translation). During translation, the ribosome needs to decode the codon of the mRNA, recruit the corresponding aminyl tRNA, and catalyze the generation of the peptide chain. The resolution of the crystal structure of ribosomes with atomic resolution has given us a molecular level insight into protein synthesis, one of the most important life processes. Some important concepts of this process, such as the high fidelity of translation and the wobbliness of the third codon, are now perfectly explained in the structure of the ribosome. The development of antibiotics based on the structure of the ribosome shows that these studies are not only of basic research interest but also have important implications for human disease therapy. Targeting the ribosome is a proven approach for disease treatment. For example, more than half of all antibiotics are known to act on the ribosome. Studies have shown that the ribosome is very sensitive to chains of amino acids being synthesized, and when an amino acid is delivered to the
catalytic site of the ribosome, it can stop the activity of the ribosome that is synthesizing a new peptide, such as under certain physiological conditions or in the presence of large amounts of an amino acid, peptide, or other compounds such as an antibiotic. Ribosomes bind persistently to tRNA and amino acids, peptides or other compounds such as antibiotics to form complexes that dock the ribosome in the open reading frame of the leading peptide mRNA being transcribed, a phenomenon known as ribosome stalling. Ribosomes are the target of many antibiotics that inhibit bacterial protein synthesis, such as macrolides, and the inability of antibiotics to bind effectively to ribosomes due to structural variation or methylation by bacterial methyltransferases is one of the important mechanisms of antibiotic resistance.\[^{64}\]

A large number of studies have demonstrated that exosomes play an important role in the process of tumorigenesis and development, and the relevant mechanisms have made good progress in the gradual exploration. Exosome-mediated cellular communication between donor and recipient cells and the modification of tumor microenvironment accelerate the malignant progression of tumors. Due to its specificity, exosomes have great potential to be used in tumor diagnosis and detection, but the isolation and purification of exosomes, and qualitative analysis of components still need to be improved and optimized, and efficient and specific biomarkers need to be further explored. In addition, as carriers of intercellular communication molecules, exosomes are rich in contents and contain a large amount of biological information, and therefore have the potential to be used as natural carriers. Compared with synthetic drug carriers, exosomes have the advantages of stable properties, immune escape, long circulation time, less side effects, ability to load a variety of drugs, specific delivery, ability to use different intracellular transport pathways, and ability to cross various barriers. Additionally, some modifications on exosomes can further enhance their targeting and drug utilization. These characteristics make exosomes a research hotspot in the development of cancer therapeutic options. However, the application of exosomes to tumor treatment requires further clarification of the mechanisms associated with the action of specific active ingredients in exosomes and tumors, and improvement of their targeting and specificity, as well as standardization of drug delivery methods and doses. Although there are still many challenges to be solved, exosomes are still of great significance for the diagnosis, therapeutic effect assessment, and prognosis of tumors. In short, exosomes play an important role in intercellular communications, and have a broad application prospect in tumor diagnosis and treatment.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

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REFERENCES

1. N. S. White, R. J. Errington, Adv. Drug Deliv. Rev. 2005, 57, 17.
2. M. H. Lee, A. Sharma, M. J. Chang, J. Lee, S. Son, J. L. Sessler, C. Kang, J. S. Kim Chem. Soc. Rev. 2018, 47, 28.
3. Y. Dong, B. Liu, Y. Yuan. J. Control Release 2018, 290, 129.
4. Y. Hong, J. W. Lam, B. Z. Tang. Chem. Soc. Rev. 2011, 40, 5361.
5. A. Melnick, J. D. Licht, Blood 1999, 93, 3167.
6. V. Lallemand-Breitenbach, H. de Thé, Curr. Opin. Cell Biol. 2018, 52, 154.
7. K. Herzer, G. Gerken, T. G. Hofmann, World J. Gastroenterol. 2014, 20, 12367.
8. K. S. Hsu, H. Y. Kao, Cell Biosci. 2018, 8, 5.
9. R. Bernardi, A. Papa, P. P. Pandolfi, Oncogene 2008, 27, 6299.
10. S. Hatakeyama, Trends Biochem. Sci. 2017, 42, 297.
11. N. Dror, N. Rave-Harel, A. Burchert, A. Azriel, T. Tamura, P. Tailor, A. Neubauer, K. Ozato, B. - Z. Levi, J. Biol. Chem. 2007, 282, 5633.
12. Y. Geng, S. Monajembashi, A. Shao, D. Cui, W. He, Z. Chen, P. Hemmerich, J. Tang, J. Biol. Chem. 2012, 287, 30729.
13. P. Salomoni, P. P. Pandolfi, Cell 2002, 108, 165.
14. A. Zelent, F. Guidez, A. Melnick, S. Waxman, J. D. Licht, Oncogene 2001, 20, 7186.
15. P. P. Pandolfi, P. P. Pandolfi, M. Alcalay, M. Fagioli, D. Zangrilli, A. Mencarelli, D. Diverio, A. Biondi, F. Cozzo, A. Rambaldi, F. Frigani, EMBO J. 1992, 11, 1397.
16. R. E. Gallagher, R. E. Gallagher, Y. P. Li, S. Rao, E. Paletta, J. Ander sen, P. Etkind, J. M. Bennett, M. S. Tallman, P. H. Wiernik, Blood 1995, 86, 1540.
17. A. Zelent, Brit. J. Haematol. 1994, 86, 451.
18. Y. Shima, Y. Honma, I. Kitabayashi, Cancer Res. 2013, 73, 4278.
19. L. Wennström, P. W. Edslev, J. Abrahamsson, J. M. Nørgaard, Y. Fleisand, E. Forestier, G. Gustafsson, J. Hedrump, L. Hovi, K. Jah- nukainen, O. G. Jonsson, B. Lausen, J. Palle, B. Zeller, E. Holm berg, G. Julliusson, D. Stockelberg, H. Hasle, Nordic Society of Paedi atric Haematology and Oncology (NOPHO), Danish Acute Leukaemia Group; Swedish Acute Myeloid Leukaemia Group, Pediatric Blood Cancer 2016, 63, 83.
20. S. Abedin, J. K. Altman, Hematol. Am. Soc. Hematol. Educ. Program. 2016, 2016, 10.
21. H. R. Chang, A. Munkhjargal, M. - J. Kim, S. Y. Park, E. Jung, J. - H. Ryu, Y. Yang, J. - S. Lim, Y. Kim, Mutat. Res. 2018, 809, 99.
22. R. Bernardi, P. P. Pandolfi, Nat. Rev. Mol. Cell Biol. 2007, 8, 1006.
23. V. Lallemand-Breitenbach, H. de Thé, Csh Perspect Biol., 2010, 2, doi: ARTN a00066110.1101/cshperspect.a000661.
24. J. Ablain, K. Rice, H. Soilihi, A. De Reynies, S. Minucci, H. De Thé, Nat. Med. 2014, 20, 167.
25. M. Niwa-Kawakita, O. Ferhi, H. Soilihi, M. Le Bras, V. Lallemand-Breitenbach, H. De Thé, J. Exp. Med. 2017, 214, 3197.
26. M. Watanabe, S. Hatakeyama, J. Biochem. 2017, 161, 135.
27. V. Suri, S. Ursuqui-Inchima, P. Roussel, D. Hernandez-Verdin, Histochern. Cell Biol. 2008, 129, 13.
28. W. Xie, T. Ling, Y. Zhou, W. Feng, Q. Zhu, H. G. Stunnenberg, I. Grummt, W. Tao, Prog. Natl. Acad. Sci. USA 2012, 109, 8161.
29. D. McStey, I. Grummt, Annu. Rev. Cell Dev. Biol. 2008, 24, 131.
30. D. Ruggiero, P. P. Pandolfi, Nat. Rev. Cancer 2003, 3, 179.
31. J. Pelletier, G. Thomas, S. Volarevic, Nat. Rev. Cancer 2018, 18, 51.
32. D. Silvera, S. C. Formenti, R. J. Schneider, Nat. Rev. Cancer 2010, 10, 254.
33. A. de las Heras-Rubio, L. Peruchó, R. Paciucci, J. Vilardell, M. E. Leonart, Cancer Metast Rev. 2014, 33, 115.
34. M. H. Vaarala, K. S. Porvari, M. C. Mustonen, O. Lukkarinen, P. T. Vikho, Int. J. Cancer 1998, 78, 27.
35. A. Bee, Y. Ke, S. Forootan, K. Lin, C. Beesley, S. E. Forrest, C. S. Foster, Clin. Cancer Res. 2006, 12, 2061.
36. E. U. H. Sim, C. H. Ang, C. C. Ng, C. W. Lee, K. Narayanan, J. Hum. Genet. 2010, 55, 118.
37. J. Kowal, M. Tkach, C. Thery, Curr. Opin. Cell Biol. 2014, 29, 116.
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