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Why is Lamin B Receptor Downregulated in Senescence?

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Abstract

An important mechanism ensuring spatial organization of chromatin structure and genome function in eukaryotic nuclei consists in anchoring of specific heterochromatin regions to nuclear envelope by proteins of inner nuclear membrane (INM) that are able to recognize these regions and simultaneously bind either Lamin A/C or lamin B1. One of these proteins is lamin B receptor (LBR) that binds lamin B1 and tethers heterochromatin to INM in embryonic and undifferentiated cells. It is replaced by lamin A/C with specific lamin A/C binding proteins (especially LEM-domain proteins) at the beginning of cell differentiation. Our functional experiments in cancer cell lines show that heterochromatin in cancer cells is tethered to INM by LBR that is downregulated together with lamin B1 at the onset of cell transition to senescence. A coordinated regulation of these proteins is evidenced also by downregulation of LB1 in cells with LBR silenced by shRNA. The downregulation of these proteins in senescent cells leads to the detachment of centromeric heterochromatin from INM resulting in it distension in nucleoplasm. These changes in structure of constitutive heterochromatin may be the reason of a permanent loss of cell proliferation in senescence.

Keywords: Lamin B receptor; Lamin B1; Lamin A/C; Heterochromatin tether; Constitutive heterochromatin; Cellular senescence; Centromere specific satellite heterochromatin

Abbreviations CSH: Centromere Specific Satellite Heterochromatin; INM: Inner Nuclear Membrane; LAD: Lamin-Associated Domain; LB1: Lamin B1; LBR: Lamin B Receptor; MN: Micronuclei; NE: Nuclear Envelope; SA-β-Gal: Senescence-Associated β-Galactosidase; SADS: Senescence-Associated Distension of Satellite; SAHF: Senescence-Associated Heterochromatin Foci

Function of Lamin B receptor in Anchoring of Chromatin to Inner Nuclear Membrane

It has been well established that spatial organization of chromatin plays critical roles in genome functions [1]. Majority of eukaryotic nuclei has a conventional nuclear architecture with euchromatin predominantly located in internal nucleus, whereas heterochromatin underlies the nuclear envelope and around the nucleolus. This functional chromatin arrangement is maintained by means of binding of peripheral heterochromatin sequences to nuclear envelope (NE). Guelen et al. [2] found that genome-lamina interaction occur in more than 1300 discrete domains dividing thus the human genome into large sharply demarcated domains about 0.1-10 Mb in size. These lamina associated domains (LADs) are characterized by repressive chromatin showing that nuclear lamina represents major structural element for organization of nuclear genome. Solovei et al. [3] identified the existence of two types of chromatin attachment to lamina: One is executed by means of lamin B receptor (LBR) in embryonic and non-differentiated cells and the other mediated by specific lamin A/C binding proteins (especially LEM-domain proteins) expressed in differentiated cells [4]. These LEM-domain proteins present a growing family of nonrelated proteins of inner nuclear membrane (INM) [5] linking this membrane and lamin A/C to chromatin during interphase. The LEM-domain proteins share some important properties with LBR: they are anchored to INM, interact with lamins and bind to chromatin and/or DNA through their binding partners [6]. LBR is a protein of INM, which preferentially binds lamin B1 and its mutations are known to cause Pelger-Huet anomaly in humans. Tudor domain of LBR selectively interacts with heterochromatin and represses transcription by binding to chromatin regions marked by specific histone modifications [7-9]. It follows from the work of Clowny et al. [10] that LBR, INM and B type lamins are able to build a heterochromatin tether. However the results of Kim et al. [11] and Yang et al. [12] indicate that B type lamins can be dispensable in this function, because cells from mice, lacking both LmnB1 and LmnB2, retain a conventional nuclear architecture in the absence of LA/C, which can be due to the presence of LBR which has several transmembrane domains for attachment to INM [3].

Distinct Types of Heterochromatin Attachment to the Nuclear Membrane in Undifferentiated (Embryonic) and Differentiated Cells

The existence of two heterochromatin tethers to INM distinguishes cells able to proliferate from cells that finished proliferation and differentiate by supporting essential organization of the structure and functions of the chromatin [13,14]. Each of these chromatin tethers is responsible for the formation of specific higher order chromatin structure and regulation of gene expression. While the chromatin structure arranged by the attachment of heterochromatin to INM by LBR in embryonic and non-differentiated cells allows active expression of genes participating on cell proliferation, heterochromatin tether executed by lamin A/C with LEM-domain proteins changes this chromatin structure to enable silencing of proliferative genes and active expression of new genes, specific for different types of

differentiated cells. This activation of cell type specific genes is assured by binding of heterochromatin to lamin A/C by the LEM-domain proteins, specifically expressed in this specific cell type. Experiments of Solovei et al. [3] show that the pattern of LEM-domain protein expression is cell type specific, while none of the LEM domain proteins seems to be universally expressed in mammalian cells. The LEM-domain proteins cooperate with lamin A/C in tethering peripheral heterochromatin to the INM and different LEM proteins and their combination mediate heterochromatin binding to lamin A/C, depending on the cell type and developmental stage [15-17]. During development and cell differentiation, LBR and lamin A/C expression is sequential and coordinated. Initially, in non-differentiated cells, only LBR is expressed while later at the onset of cell differentiation it is replaced by lamin A/C. Expression of both these proteins in differentiated cells is only rarely seen. Experiments in knock out mouse showed that in most cell types, deletion of lamin A/C is compensated by prolonged expression of LBR [3]. However, no data are available showing attachment of heterochromatin to lamina in senescent cells.

Lamin B is Down-Regulated in Senescence

Cellular senescence is a cellular response to a variety of stress [18-20]. It is accompanied by a set of characteristic morphological and physiological features that distinguish senescent cells not only from proliferating cells, but also from quiescent or terminally differentiated cells [19,20]. Because senescence plays the important role in both normal physiology and diverse pathologies it is important to well understand its molecular bases. Typical features of senescence are irreversible proliferation arrest, enlarged cellular morphology, expression of senescence-associated β-galactosidase activity (SA-β-gal) [20], enhanced nuclear heterochromatinization [19], senescence associated secretory phenotype [21,22] and DNA damage signaling [23,24]. These senescence attributes are generally manifested by cells in replicative senescence (due to telomere shortening) [25] and the so-called premature senescence, due to different stressors such as oxidative stress and other DNA damaging insults [26,27] and activated oncogene [27,28].

The onset and maintenance of the senescent state involve action of two major tumor suppressive pathways, p53-p21 and p16ink4a-pRb [29,30]. Up-regulation of p16INK4a is particularly prevalent in benign lesions, is often lost upon malignancy [31] and its expression can be dispensable in senescence [32,33]. Most known senescence-associated markers were obtained in studies of oncogene-induced senescence or replicative senescence in human diploid fibroblasts [19,34]. They include large senescence-associated heterochromatin foci (SAHF) enriched in heterochromatin markers, such as

H3K9me3 and HP1 proteins. However, SAHF formation does not occur in all senescent cells [28]. They are absent, for example, in human mammary carcinoma MCF7 and fibrosarcoma U2OS cells in which the senescence was induced by γ-irradiation [33] or by inhibition of replication and Chk1 kinase.

In recent years, it was reported that lamin B1 (LB1) expression is reduced in replicative and oncogene-induced senescence, which delays cell proliferation and promotes cellular senescence via a p53- and Rb-dependent mechanism [35-38]. Chandra et al. [39] observed that areas that have lost LB1 in senescent cells are enriched by lamina-associated domains (LADs), suggesting that the loss of LB1 might be involved in the architectural changes to chromatin and formation of SAHF that they studied earlier [40]. Independently, Sadaie et al. [41] showed that LB1 is preferentially depleted during senescence from the chromatin regions containing LADs enriched for H3K9me3, a characteristic for constitutive heterochromatin, which promote the formation of SAHF. In addition, these authors observed, despite the global reduction in LB1 level, the increased binding of this protein with gene-rich regions where H3K27me3, characteristic for facultative heterochromatin, increased. However, there are not known specific reader sequences of LB1 for the recognition of lysine-methylated residues of chromatin. The recognition of these sequences ensures LBR at joining with LB1 as found earlier [9]. We observed LB1 foci of variable size scattered through the chromatin in some senescent nuclei of MCF7 and U2OS cells [33] and assume that these foci might represent protein degradation centers [42].

The Onset of Senescence is accompanied by a Coordinated Downregulation of Lamin B Receptor and Lamin B1 Expression

Our results show down-regulation of both LBR and LB1 at the onset of senescence induced by γ-irradiation of two cancer cell lines (MCF7 and U2OS) [33]. We attempted to find out why these proteins down-regulation occurs by studying the role of LBR in the attachment of centromere-specific satellite heterochromatin (CSH) of gene-poor and gene-rich chromosomes to INM in cycling cancer cells and after the transition of these cells to senescence. We observed that a high fraction (≤ 80%) of CSH of heterochromatin-rich (gene-poor) and about 50% of heterochromatin-poor chromosomes co-localized with the INM in these cancer cells and more than half of these sequences detached from the lamina and relocalized to the nucleoplasm where they were decondensed, not only in the beginning of senesce, where LBR and LB1 were lost, but also in cells where LBR expression was reduced by LBR specific shRNA. Colocalization of CSH with the INM also decreased significantly, by approximately two-thirds, in heterochromatin-rich and by one-third in euchromatin-rich chromosomes in cells with shRNA-reduced expression of LBR. These results confirmed the role of LBR as a constitutive heterochromatin tether in proliferating cancer cells [3,9,10]. Moreover, nuclei of senescent cells showed elevated numbers of centromeric signals in different cell lines suggesting that detachment of centromere specific satellite heterochromatin from lamina and its decompaction in nucleoplasm may induce endoreduplication of this chromatin. Results showing the detachment of CSH of chromosomes with the prevailing amount of heterochromatin (mainly of chromosome 18) from lamina in cells with reduced expression of LBR and LB1 are in consensus with the results of Malhas et al. [43], which showed that an absence of LB1 or its full length protein resulted in relocation of chromosome 18 from the nuclear periphery to the nuclear center in mouse embryonic fibroblasts, followed by decondensation of this chromosome and changes in expression of some of its genes. No changes were observed in chromosome 19, located in the center of these cells' nuclei. Even if the authors did not follow changes in LBR level, it could be supposed, on the basis of our results, that in the absence of LB1 or in the presence of its incomplete structure, the heterochromatin tether, executed in these embryonic cells by LBR [3], cannot be performed resulting in the exchange of a normal location of chromosome 18 from the nuclear membrane to the nuclear center.

LBR protein is known to contain specific regions for heterochromatin attachment, recognition of specific histone methylations and, in addition, the attachment of LB1 [7,9,44-46].The role of LBR in un- or early differentiated state of cells is demonstrated

also in experiments of Clowney et al. [10] showing that transgenic expression of LBR deregulates the differentiation of olfactory neurons. The binding of LBR, but not LB1 to heterochromatin also follows from the stability of LBR associated with condensed chromatin and the INM during the late stage of apoptosis, while lamin B1 is proteolysed at an early stage [47]. The protease resistance of this LBR association, which plays a major role during apoptosis, is also likely to be important in nuclear membrane reassembly in late anaphase [48]. The functional dependence of LB1 on LBR results from current down-regulation of this protein at reduced expression of LBR by LBR-specific shRNA shown in our experiments [33]. However, down-regulation of both these proteins by LBR shRNA did not induce senescence. Clones of MCF7 and U2OS with reduced expression of these proteins exhibited slower proliferation compared with the parental cells, formed higher numbers of micronuclei (MN) showing higher permeability of the nuclear membrane, and were transferred to senescence by γ-irradiation similarly to their parental cells. Even if it seems that the down-regulation of LBR and LB1 is necessary for cell transition to senescence, it does not elicit this process.

It follows from these results that LBR and LB1 together form a functional unit in which LBR recognizes specific nucleotide sequences and histone modifications for heterochromatin organization, transcription repression, and anchoring to the INM. LB1, which is attached to LBR in its globular domain II, probably represents some kind of matrix for LBR, distributing this protein in the lamina and directing it to the chromatin regions containing specific lysine-methylated residues that should be condensed and attached to INM. Thereby, a specific chromatin structure is set and conditions are established for active transcription, including genes responsible for cell proliferation in undifferentiated, cycling cells [3,9].

Consequences of LBR Down-Regulation in Senescence

The down-regulation of LBR and LB1 in the beginning of senesce results in the detachment of centromeric heterochromatin containing the H3K9me3 modification from lamina, relocation to the nucleoplasm and distension showing that this down-regulation of LBR and LB1 is necessary for the release of heterochromatin from binding to the lamina, to achieve changes in chromatin architecture and regulation of gene expression leading to stop of cell proliferation. Distension of peri/centromeric satellite sequences in different human fibroblasts induced to senescence by diverse stresses observed also Swanson et al. [49] and called them "Senescence-associated distension of satellite (SADS)". This observation indicates that the phenomenon of centromeric heterochromatin decompaction is common phenomenon in senescence. The cause of this phenomenon is loss of the heterochromatin tether showing its importance for maintaining chromatin structure and function.

Peri/centromeric heterochromatin represents a large part of constitutive heterochromatin in human genome in which is located a large number of LAD domains attached to INM by LBR-LB1 tether in embryonic and undifferentiated cells. Decompaction of this heterochromatin put these LAD domains out of function and makes their use in the attachment to lamina impossible. It indicates that resumption of proliferation in these cells is no longer possible. In addition the loss of constitutive heterochromatin structure could influence chromatin architecture and function in all nucleus. While the heterochromatin tether executed in embryonic cells by LBR is, after downregulation of this protein at the beginning of cell differentiation, replaced by lamin A/C with specific LEM-domain proteins, there is not known any heterochromatin tether after down-regulation of LBR at transition of cells to senescence. The cause may be just the loss of constitutive heterochromatin structure.

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Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

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