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Review Article

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The Long Non-Coding RNA SENEBLOC

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Abstract

Cellular senescence is a stress response and a permanent state of cell cycle arrest of normal cell division. SENEBLOC is involved in both oncogenic and replicative senescence and has been identified as a c-Myc responsive lncRNA involved in senescence. SENEBLOC acts to restrains p21-mediated senescence. Mouse double minute 2 (MDM2) regulates p53, controls its transcriptional activity and protein stability. Cyclin-dependent kinase (CDK) inhibitor p21 promotes cell cycle arrest in response to a variety of stimuli and it can be induced by both p53-dependent and p53-independent mechanisms. SENEBLOC is shown to drive both p53-dependent and p53-independent mechanisms. SENEBLOC acts as a scaffold to promote p53 turnover. It decreases p21 transactivation and promotes p53 and MDM2 association. p53-independent regulation of p21 by SENEBLOC occurs via regulatory effects on HDAC5. Rapamycin promotes SENEBLOC transcription through effects on E2F1. In this review, I focus on the importance of the newly identified LncRNA SENEBLOC.

Keywords

Senescence;LNCRNA SENEBLOC;P53;P21;HDAC5.

Introduction

Long-non-coding RNAs (lncRNAs) are RNA molecules longer than 200 nucleotides [1], involving in diverse biological processes, including but not limited to cardiovascular physiology, reproduction, differentiation, metabolism, DNA repair, and inflammation [2]. LncRNAs are dysregulated in different kinds of cancer [3], and may exhibit tumor-suppressive and -promoting (oncogenic) functions [4]. They are involved in cell apoptosis, cell metastasis, and invasion, epithelial-mesenchymal transition (EMT), cancer stem cells (CSCs) [5]. Non-coding RNAs conduct the major senescent pathways (p53/p21 and pRB/p16), the senescence-associated secretory phenotype (SASP), and other senescence-associated events [6]. SENEBLOC is a newly identified long non-coding RNA and is expressed in normal and transformed cells under homeostatic conditions [7]. SENEBLOC acts as a scaffold to promote p53 turnover. It decreases p21 transactivation and promotes p53 and MDM2 association [7]. SENEBLOC is shown to drive both p53-dependent and p53-independent mechanisms [7]. The cell cycle involves numerous regulatory proteins [8]. Gene silencing of tumor suppressor and growth-inhibitory genes is frequently mediated by DNA methylation of gene promoters [9].

Central to this process are the cyclin-dependent kinases (CDKs), which complex with the cyclin proteins [8]. Downstream targets of cyclin-CDK complexes include pRb and E2F [8]. p21(Waf1) a protein that suppresses cyclin E/A-CDK2 activity [10]. p21(Waf1) is involved in the regulation of fundamental cellular processes, such as cell proliferation, differentiation, migration, senescence, and apoptosis [10]. The functions of p21(Waf1) depends on its intracellular localization. When p21(Waf1) is localized in the cytoplasm, it acts as an oncogene by regulating apoptosis, proliferation, and migration [10]. The p53 gene is important in controlling the cell cycle, apoptosis, and DNA repair. The cyclin-dependent kinase inhibitor p21WAF1/CIP1, which is downstream of p53, is regulated by both p53-dependent and p53-independent pathways [11, 12]. In the G1 phase, the p53-dependent arrest of cells is important for the cellular response to stress [11]. p53 signaling, mammalian target of rapamycin, nuclear factor-κB (NF-κB), and transforming growth factor-beta are several important signaling pathways of cellular senescence [13]. Rapamycin shows antagonistic actions on p21 expression and this is dependent on SENEBLOC [7]. Mouse double minute 2 (MDM2) is a critical negative regulator of the tumor suppressor p53 [14], can ligate the p53 protein via its E3 ubiquitin ligase [15]. Targeting the interaction between p53 and MDM2 is an attractive treatment approach for cancers [16]. Xu et al shows that SBLC (AL161785.2) is located on chromosome 9 (132,020,633-132,022,125) with the annotated transcript (RP11-344B5.4) comprised of three exons [7].

Oncogene expression and telomere shortening are different stimulators of cellular senescence [17]. Aberrant activation of oncogenic signaling results in oncogene-induced cellular senescence (OIS) [18]. In response to oncogenic stimuli, senescence suppresses cancer by arresting cell proliferation, essentially permanently [19]. SENEBLOC is related to both oncogenic and replicative senescence [7]. Cellular senescence can be triggered by a number of factors including, aging, DNA damage, oncogene activation, and oxidative stress [20]. Molecular mechanisms of senescence involve 16 and p53 tumor suppressor genes and telomere shortening [11]. Epigenetics is the study of heritable alterations in gene expression [21], and three interlinked epigenetic processes regulate gene expression at the level of chromatin, these are DNA methylation, nucleosomal remodeling, and histone covalent modifications [21]. Abnormal methylation patterns of DNA and modifications of histones in chromatin contribute to disease [22]. Regulators of epigenetic programs, such as histone acetyltransferases (HATs) and histone deacetylases (HDACs), are known to play an important role in gene expression [23]. HDAC enzymes are grouped into four different classes [21]. Class I enzymes include HDAC1, HDAC2, HDAC3, and HDAC8; Class II enzymes that include HDAC4, HDAC5, HDAC6, HDAC7, HDAC9, and HDAC10, and Class III HDAC and Class IV (HDAC11) [21]. p53-independent regulation of p21 by SENEBLOC occurs via regulatory effects on HDAC5 [7]. SBLC facilitates p53-independent regulation of p21 through miR-3175-dependent effects on HDAC5 [7].

Retinonablastoma (RB) is an important regulator of G1 / S cell cycle progression [24]. Genetic and epigenetic changes cause impairment in pRB function, which leads to the release of E2F1 and its transcriptional activity. Functional inactivation of pRB and subsequent deregulation events of E2F1 are essential steps in tumorigenesis [25]. E2F1 (E2 promoter binding factor 1) is a transcription factor involved in cell cycle regulation, apoptosis, DNA-

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damage response [26-28]. E2F1 exhibits dual properties, acting as a tumor suppressor and oncogene and its transactivation capacity is regulated by the retinoblastoma protein (pRb) [26, 29]. Cell division cycle in mammalian cells is regulated by E2F transcription factors and the retinoblastoma protein [30]. The retinoblastoma protein (pRB), has the dual capability to negatively regulate both E2F-induced cell cycle entry and E2F1-induced apoptosis, interacts with E2F during controlling cell cyle and apoptotic processes [31, 32]. The Rb protein is a tumor suppressor that has crucial functions in in the negative control of the cell cycle [33]. Rapamycin promotes SBLC transcription through effects on E2F1 [7]. Rapamycin promotes SBLC transcription through effects on E2F1 [7]. Xu et al showed that there are potential binding motifs for a number of transcription factors within the SBLC promoter including E2F1, USF1, MAZ, SP1 and CREB1 [7].

c-myc is one of a small family of proto-oncogenes [34], encodes the transcription factor c-Myc [35]. Deregulated activity of c-Myc is related with many human cancers [36], c-Myc controls the regulation of many non-coding (nc) RNAs, including tRNA, rRNA and miRNAs [36]. The regulation of p53 and c-Myc network is coordinated in almost every crucial decision of almost every cell [37]. Recent findings show that there is an interplay between lncRNAs and MYC in cancer [38]. LncRNA-MYC network has significant roles in regulating initiation, development, and metastasis of tumors [38]. The multifunctional protein c-Myc also affects the stability of the genome [34]. Deregulated c-myc expression generates genomic instability by initiating gene rearrangements, gene amplification (both intra- and extra-chromosomally), and karyotypic instability [34]. MYC expression is also controlled and regulated at the level of protein and mRNA stability [39]. Overexpressed c-MYC results in the onset of many hallmarks of cancer [40]. SENEBLOC has been identified as a c-Myc responsive lncRNA involved in senescence. SBLC expression is controlled by transcription factor c-Myc and LncRNA SBLC is directly regulated by c-Myc. SBLC is shown as a c-Myc responsive lncRNA involved in evasion of senescence. Over-expressed c-Myc was also found to increase the level of SBLC. Multiple c-Myc consensus binding sites (c-Myc-BS) in its proximal promoter and between exons 1 and 2 has been shown [7].

Conclusion and perspectives

LncRNAs are important regulators of biological responses, and they are dysregulated in many cancer [2, 3]. Oncogenic genes and oxidative stress, which cause genomic DNA damage and generation of reactive oxygen species, lead to cellular senescence [13]. Senescence is an irreversible cell-cycle arrest with a crucial role both in aging and in physiological antitumor response [41]. The cell cycle is regulated by proteins and in this process, p21(Waf1) has central functions, such as regulating cell proliferation, differentiation, migration, senescence, and apoptosis [8, 10]. HDAC enzymes are well-known histone deacetylases with regulatory functions in gene expression and SENEBLOC affects epigenetic silencing of the p21 gene promoter through regulation of HDAC5 [7, 23]. SENEBLOC decreases p21 transactivation and promotes p53 and MDM2 association [7]. Further studies on SENEBLOC may shed light on understanding the molecular mechanisms of disorders.

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