

## Myelodysplastic Syndrome-Related Hematopoietic Stem Cell Diseases

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### Abstract

Cellular senescence's role in the course and prognosis of Myelodysplastic syndrome CD34+ or bone marrow mononuclear cells from MDS, acute myeloid leukaemia, and healthy controls were examined for p16INK4a expression. Quantitative senescence-associated -galactosidase staining of MDS and AML patients' bone marrow mononuclear cells, the leukaemia cell lines HL60 and SHI-1, and healthy control cells was also examined. When contrasted with solid people, the declaration of the senescence-related hereditary marker p16INK4a was demonstrated to be raised in MDS, while it was viewed as down regulated in AML. Our current investigation revealed that MDS accelerated cellular senescence, which may play a role in the disease's progression and prognosis.

**Keywords:** Myelodysplastic syndrome; Cellular senescence; Preneoplastic stage of blood cell; Fluorescence

### Introduction

A group of hematopoietic stem cell disorders known as "Myelodysplastic syndrome" have a high risk of developing acute myeloid leukaemia and inadequate haematopoiesis, which causes blood cytopenias. The morphology and impact cell rate in the blood and bone marrow can be utilized to order AMMDs. The most important prognostic factors for MDS include the proportion of marrow blasts, the frequency and severity of cytopenias, and cytogenetic abnormalities in the bone marrow [1]. These variables are combined in an International Prognostic Scoring System (IPSS) to divide patients into four subgroups: high-risk, intermediate I (int I), and intermediate II (int II). Patients with MDS regularly create clear AML, especially assuming they have the MDS-unmanageable sickness with overabundance impacts (RAEB) subtype.

### Method

The cyclin-dependent kinase inhibitor p16INK4a gene at 9p21 is associated with the cell cycle. It produces the p16INK4a protein, which competes with the cyclin-dependent kinase protein during the G1 phase of the cell cycle. In a variety of human cancers, the p16INK4a protein is frequently overexpressed and inactivated in cultured senescent cells. As a result, the senescence marker p16INK4a, previously identified as a tumor suppressor gene, has been discovered. Oncogene-induced senescence, a cellular response, may be necessary to stop cancer from growing [2]. Oncogene-induced senescence occurs in a high percentage of cells in premalignant tumors. In order to support our previous theories regarding the preneoplastic stage of blood cell cells in MDS, we examined the expression of p16INK4a in patients with MDS to determine whether cellular senescence developed in MDS, whether it may be related to the progression of the disease, and whether it may be related to the patients' prognoses. The BM single-nuclear cell fraction was separated through density gradient centrifugation using Ficoll-Paque PLUS.

Before using bright-field microscopy to examine the cells, slides that had been stained with SA-gal were counterstained with Wright-Giemsa solution. To compute the level of senescent dysplastic cells in M-D and senescent cells in charge and AML tests, the Wright-Giemsa-stained spreads went through morphological assessment for dysplastic cells and typical cells [3].

Patients' or cell lines' cells were permitted to stick to polylysine-L coverslips prior to being fixed at room temperature in paraformaldehyde.

Subsequent to washing in PBS and permeabilizing the cells with sodium dodecyl sulfate (SDS) 0.1% for 10 minutes, the cells were then stained with the suitable measures of the essential antibodies against p16INK4a and envisioned utilizing red fluorochromes. The cells' DNA was counterstained with 6-Diamido-2-phenylindole. By centrifuging, insoluble materials were wiped out. The samples were measured using a Bio-Rad protein assay kit II (Bio-Rad, Hercules, CA, USA) after being boiled for five minutes in an SDS sample buffer prior to SDS-polyacrylamide electrophoresis. After electrophoresis on SDS-polyacrylamide gels [4], the proteins were moved to polyvinylidene difluoride layer. St Nick Cruz Biotechnology was utilized for the acquisition of the counter p16INK4a antibodies. St Nick Cruz Biotechnology provided the horseradish peroxidase-formed and hostile to actin antibodies.

### Results

It has been suggested that SA-gal can be used as an in vivo and in vitro marker for cell senescence. The SA-lady staining of BMMNCs from MDS and AML patients, HL60 and SHI-1 leukemia cells, as well as should be expected control cells, has been assessed. MDS cells had a strong stain of SA-gal activity. These SA-lady positive cells had leveled shapes and expanded sizes, which are indications of senescence [5]. Based solely on morphological criteria, the majority of SA-gal positive cells belonged to differentiated myeloid cells. The SA-gal activity, as indicated by the mean percentage of positive cells, was significantly higher when MDS cases were compared to controls. In cases of MDS, M-D cells had a significantly higher proportion of SA-gal-positive cells than non-M-D cells. The SA-gal activity, on the other hand, decreased in AML cases, as indicated by the mean percentage of positive cells. Then again, cells from MDS showed an essentially more extraordinary SA-lady staining that was limited and even multifocal, as well as a higher extent of stained cells that were positive. Cells from controls showed a gentle blue staining for SA-lady action, in the interim [6].

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## Discussion

Cellular senescence, which is thought to be mediated by either telomere-dependent or telomere-independent processes or results in cell cycle arrest, is thought to be the response of proliferating cells to stress and injury. Telomere-independent processes include oncogene- or reactive oxygen-induced senescence. Oncogene-induced senescence was once thought to be caused by Ras oncogene expression. The p53 and p16-pRB pathways were accountable for controlling cell senescence. Oncogenic RAS is one example of a input that activates both pathways. Oncogenic Ras articulation causes a G1 capture that is industrious and is trailed by a development of p53 and p16. It is believed that cellular senescence is a protective mechanism that may prevent diseased or aged cells from expanding further. SA-gal activity and p16INK4a have been identified as senescence markers. Beginning phase human prostate disease biopsy tests likewise contained the senescent districts of SA-lady positive staining to the improvement of MDS should be visible as a precancerous condition since it is a consequence of the ever-evolving change of solid platelets into leukemia cells. Based on the intriguing idea that a senescence mechanism could have an impact on and reflect on various MDS phases [7].

The majority of MDS patients have normal or hypercellular marrow but exhibit peripheral blood cytopenia. Increased hematopoietic progenitor apoptosis has been identified as the cause of this contradiction. It has been found that apoptosis has decisively risen, which might demonstrate a pathophysiological system in the beginning phases of sickness [8]. Cell senescence may also play a role in the hematopoietic system's stagnation or even failure, as does apoptosis. The effective tumor-suppressing mechanisms of oncogene-induced senescence and apoptosis may prevent injured cells from undergoing neoplastic transformation. The planning of these two organic cycles' activities in beginning phase MDS, as well as their linkage and transaction, are as yet unclear. Understanding the mechanism by which MDS progresses to AML will be made easier if we accept the hypothesis that precancerous cells that have been in senescent status for a variety of periods of time may escape and accelerate growth to undergo malignant transformation. The MDS-induced cellular senescence was brought on by these abnormally activated oncogenes.

Dysplastic cells' clonal beginning. The alleged dysplasia of BM cells in MDS is their most distinctive trademark. This unusual MDS cell population's underlying biology is currently unknown. Aberrant karyotype MDS-refractory anemia may exhibit more obvious and varied dysplasia than control groups. Fluorescence in situ hybridization, which was carried out on MDS patients with clonal cytogenetic anomalies by another group in our institute, revealed that the dysplastic cells in MDS are primarily derived from the aberrant clone. In comparison to control cells, the percentage of SA-gal-positive cells in MDS was noticeably higher. The proportion of SA-gal-positive cells in dysplastic cells was noticeably higher when compared to the absence of dysplastic cells in the MDS bone marrow material. Additionally, MDS-no-dysplastic cells had a higher proportion of SA-gal-positive cells than control cells [9]. These findings demonstrated that the dysplastic cells in MDS comprised a population that became more easily senescent, despite the

fact that MDS cell senescence was only somewhat related to dysplasia. As MDS accelerates cell senescence, we are attempting to comprehend the significance of senescence in the MDS development mechanism by examining the relationship between dysplastic and senescent cell populations. Because the expression of the p16INK4a protein in MDS cells was clearly higher than in controls, it is thought that the patients' prognosis is related to the activation of the p16INK4a gene. In accordance with our findings, biopsy samples taken from in situ melanocytic nevi revealed significant SA-gal activity. Notably, neither of these two markers for cellular senescence is highly expressed in leukaemia cells in comparison to MDS, regardless of cell line or primary bone marrow cells. This finding may provide some clues regarding the mechanism by which MDS cells transform into leukemia cells [10].

## Conclusion

All things considered, our current findings lead us to believe that, regardless of clonality, MDS patients' cell populations experience an accelerated cellular senescence. To comprehend the pathogenic component behind this ailment, it will be critical to distinguish and describe this subgroup of senescent cells and track their set of experiences during the beginning and movement of MDS.

## Acknowledgment

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## Conflict of Interest

None

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