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Invited Mini Review

Cellular senescence in cancer

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Cellular senescence, a process of cell proliferation arrest in response to various stressors, has been considered to be important factor in age-related disease. Identification of senescent cells in tissues is limited and the role of senescent cells is poorly understood. Recently however, several studies showed the characterization of senescent cells in various pathologic conditions and the role of senescent cells in disease progression is becoming important. Senescent cells are growth-arrested cells, however, the senescence associated secretory phenotype (SASP) of senescent cells could modify the tissues' microenvironment. Here, we discuss the progress and understanding of the role of senescent cells in tissues of pathologic conditions and discuss the development of new therapeutic paradigms, such as senescent cells-targeted therapy. [BMB Reports 2019; 52(1): 42-46]

INTRODUCTION

When cells continue to divide by repeated subculture, progressive telomere erosion occurs, the cells are no longer able to divide, and the proliferation is permanently stopped (1, 2). This phenomenon is called cellular senescence and can be observed not only *in vitro*, but also *in vivo* (1-4). Since cellular senescence was first described, studies to identify and clarify the roles of senescent cells have been undertaken (5-7). The fact that normal cells can become senescent cells by replication contrasts with the infinite proliferative ability of cancer cells (8). Therefore, normal cells that have been induced into senescence become important in physiological and pathological processes, and the role of senescent cells has become increasingly emphasized (8). Generally, senescent cells are observed as human beings age (1, 2). However, senescent cells are also observed in normal organ development and pathological conditions related to aging. For example, these cells have been observed not only in normal finger digit development, but also in examples of aging pathology, such as cataracts, osteoarthritis and atherosclerosis (9-13). Thus, most of the research on senescent cells has been conducted in primary isolated normal cells, and *in vitro* studies have induced cellular senescence mainly through DNA stimulation or subculture of fibroblasts (1, 6, 8). Recently, cellular senescence has been observed in tumor tissues (7, 14), however, the role of these cells in lesions is still poorly understood.

The role of senescent cells has been studied in recent years. The purpose of senescence is thought to be the elimination of unwanted cells, such as damaged cells (1, 6, 7). In general, transient induction of senescence in damaged tissues is considered to be a process beneficial to tissue regeneration (15, 16). However, the persistence of senescent cells or failure of their elimination, affects tissues by alteration of their microenvironment (14, 17, 18). This is related with cancer and senescence, which is characterized by accumulation of damaged and stimulated cells. Therefore, senescence is believed to be a crucial barrier against cancer progression (19-21). And recent studies reported that senescent cells may be involved in cancer progression (22-24). These senescent cells are thought to originate from tumor cells, and are called senescent tumor cells (25-28). In this review, we focus specifically on the identification and pathological role of senescent cells in the tumors.

IDENTIFICATION OF SENESCENT CELLS *IN VIVO*

Identification of senescent cells *in vivo* has technical limitations. *In vitro*, morphologic characteristics of cellular senescence are easily observed. Cells appear enlarged, flattened, and granulated, and cell growth rate decreases (1, 5, 6, 29). However, *in vivo*, senescent cells appear normal and lack such morphological changes (25-28). Therefore, senescence cellular markers have emerged as a tool for *in vivo* identification of senescent cells (30, 31). Senescence associated β-galactosidase (SA-β-Gal) staining and $p16^{INK4A}$ immunostaining have been considered as effective markers of cellular senescence (25-28). The SA-β-Gal staining method is relatively easy and provides reliable data for *in vitro* identification, as well (31). SA-β-Gal staining *in vivo*, however requires fresh frozen tissue preparation, necessitating cooperation between surgeons and pathologists (25-28). In addition, one of the things to note in SA-β-Gal staining *in vivo*

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is that it can be stained in normal tissues. Not only the senescent cells, but also some cells in specific areas of normal tissues can be stained by SA-β-Gal (30). For example, senescent fibroblasts in aged skin show SA-β-Gal positivity, but staining is also strongly observed in normal hair follicles (31, 32). SA-β-Gal also stains the mucus in normal colon epithelium (33). Nevertheless, SA-β-Gal staining is widely used to identify senescent cells *in vivo*, but, because of above strict tissue preparation requirements, the combination of SA-β-Gal with other molecular markers of senescence in the same cells provides more reliable data (30, 31). Other surrogate markers of senescence are the DNA damage signal related proteins or secreted proteins, such as γH2AX, senescence-associated heterochromatin foci (SAHF), $p21^{WAF1}$, $p16^{INK4A}$, macroH2A, interleuikin-6 (IL-6), and IL-8 (6-8, 34, 35). However, measuring senescent cells using only these markers may result in erroneous conclusions because $p21^{WAF1}$ can be fully expressed, not only senescent cells, but also in acutely DNA damaged cells (36, 37). UV exposed skin tissues show marked upregulation of $p21^{WAF1}$ expression in keratinocytes, without cellular senescence (38). In the case of $p16^{INK4A}$, a powerful and reliable senescence marker, it is strongly expressed not only when senescence is induced, but also as a result of $p16^{INK4A}$ mutation or HPV suppression (39, 40). Furthermore, IL-6 and IL-8 can also be induced by various immune responses (41, 42). Thus, rather than measuring senescence with a single marker, using a variety of methods, such as staining with both SA-β-Gal and $p16^{INK4A}$ can be a more useful way to identify senescent cells *in vivo* (25-28).

SENESCENCE ASSOCIATED SECRETORY PHENOTYPE (SASP) IN SENESCENT CELLS

An important feature of senescent cells is that their growth is arrested, but they remain metabolically active (1). Although cell proliferation is inhibited, the cells actively produce many kinds of proteins. Senescent cells are characterized by secretion of many proteins (43, 44). They express IL-6 and IL-8, which are inflammatory cytokines, as well as chemokines that attract inflammatory cells (41, 42, 44). Expression of matrix metalloproteinases (MMPs) that alter the extracellular matrix is high in senescent cells (28, 45, 46). Secretion of these different proteins can affect the surrounding neighboring cells or cause changes to the tissue microenvironment (14, 17, 18). This phenomenon is called senescence associated secretory phenotype (SASP) (18, 43). The expression pattern of the SASP is known to be different, depending on the origin of the cells. The SASP expression pattern is different between epithelial and mesenchymal cells, so SASP's influence on each tissue's microenvironment is thought to be different (18, 43). The differential expression of SASP suggests that senescent cells are actively involved in the pathogenesis of various diseases and disease progression. For example, inflammation has been observed to progress in aged tissues, without evidence of pathogenic infection, suggesting that senescent cells are involved in the inflammatory response through SASP expression (18, 47). The expression pattern of SASP is different according to the stimuli of induction, as well. For example, the SASP expression pattern is different between replicative senescence (RS), stress induced senescence (SIS), and oncogene induced senescence (OIS) (6). It has also been reported that the expression of SASP varies widely, depending on the origin of the cells (18, 43). Therefore, when senescent cells are observed in tissues, the pattern of expression of SASP varies depending on the stimuli and origin of senescent cells, and the microenvironmental effects of senescent cells in these tissues may be different (18, 43, 47).

Cellular senescence the characteristics of a double edged sword; SASP can have a positive or negative effect on disease progression (18, 43, 47). Positive factors include local wound healing, tissue regeneration from damaged cells, and immune reaction inhibition in damaged cells, processes that aid the healing process (48). SASP can also enhance the expression of MMPs in pathologic conditions, such as hepatic or skin fibrosis, preventing fibrosis during the healing process of liver damage or skin wound injuries (49). The SASP cytokines, IL-6 and IL-8, also reinforce senescence growth arrest in some senescent cells (34, 35). Negative effects include an increased inflammatory response, stimulating the growth of nearby malignant cells, and inducing metastasis of malignant cancer cells (23, 24, 28). It has also been observed that the SASP can cause an epithelial mesenchymal transition (EMT) phenomenon that promotes cancer (46, 50). Therefore, depending on the tissue structure and tissue microenvironment, SASP may be beneficial to the disease progression or may have a negative impact. It is also believed to affect disease progression, depending on the type of SASP expression. Whether the role of SASP in cancer development or cancer progression is positive or negative remains controversial.

SENESCENT CELLS IN TUMOR TISSUES

The history of senescent cell observation in tumor tissues has not been long. It was thought that senescent tumor cells would not be found in malignant tumors because of the decreased ability of senescent cells to divide (7). Recently, however, with the discovery of various markers of cellular senescence and the rapid processing of fresh tumor tissues, large numbers of senescent cells were reported in a tumor mass (25-28). Then, the question arises regarding the origin of senescent cells in tumors. To investigate this, characterization of senescent cells using various senescence, epithelial and mesenchymal cells markers was performed (28). Senescent cells in the tumors tissues were mainly observed with $p16^{INK4A}$ immunostaining and SA-β-Gal staining in $p16^{INK4A}$ non-deleted and non-mutated tumors (28, 39, 40). SA-β-Gal and $p16^{INK4A}$ staining were observed in the tumor mainly, and were considered to be senescent tumor cells. However, vimentin, a fibroblast marker,

did not stain the cells, indicating that the tumor cells had undergone senescence (7, 8, 28).

Senescent tumor cells have been thought to have the ability to inhibit tumorigenesis, since their proliferative capacity is suppressed (19-21). Senescence is induced by activation of various oncogenes, resulting in the expression of $p16^{INK4A}$ and induction of oncogene-induced senescence, and is observed in normal primary cells, including fibroblasts, melanocytes, and thyrocytes. Therefore, senescence has been considered a mechanism to inhibit cancer development (21, 49, 51). In addition, the disappearance of tumor suppressor genes, such as $p16^{INK4A}$, p53, and $p21^{Waf1}$ has been shown to induce cancer development *in vitro* (7, 19, 20). For these reasons, the presence of senescent tumor cells is thought to have a cancer suppressing effect (19-21). The discovery of senescent cells *in vivo* after oncogene activation has been reported in mouse experiments. In the $K\text{-}Ras^{G12V}$ mutant transgenic mouse, a large number of senescent cells with SA-β-Gal staining positivity were observed in the lung adenoma, and no senescent cells were found in carcinoma stage (52). In addition, melanoma formation was not observed when the $B\text{-}Raf^{V600E}$ oncogene was overexpressed in primary isolated melanocytes, and a $B\text{-}Raf^{V600E}$ mutation was observed in skin benign tumor nevus, indicating that senescent cells remained in the precancerous region (53). Furthermore, the K-Ras mutant is able to augment growth of breast cells in mouse, but it does not lead to the formation of carcinoma (54). These results present evidence that senescence limits the progression of tumor development. However, recent evidence indicates that cellular senescence or senescent tumor cells can promote carcinogenesis by producing various growth factors, cytokines, and proteases, collectively referred to as senescent-associated secretory phenotypes (23, 24, 28, 43). Although senescent cells are rarely observed in cancers tissues, the existence of senescent tumor cells in cancers has been reported (25-28). Senescent tumor cells are observed in various carcinomas such as thyroid, breast, stomach and colorectal cancer (25, 51, 55, 56). Interestingly, in some carcinomas, the distribution of senescent tumor cells is not even, and it is observed in a specific tumor tissue locations. Senescent tumor cells do not exist in the center of the mass where hypoxic damage usually occurs, but rather in the marginal region of the tumor (28). Furthermore, they are present in large numbers in the metastatic lymph nodes and lymphatic vessels (28). These data demonstrate that senescent tumor cells are actively involved in cancer progression and SASP expression is thought to be involved in that process (28). Senescent tumor cells express SASP and their SASP expression patterns are different than those of senescent cells induced from normal cells, such as fibroblasts (6, 43). The expression pattern of SASP is similar in some proteins, but others differ between senescent tumor cells and senescent fibroblasts. For example, IL-6 and IL-8, common inflammatory cytokines, are increased in both cases, but the expression of chemokines and protease are different (28, 32, 43). The expression of matrix metalloproteinase (MMP) is markedly increased, and a large amount of protein capable of degrading extracellular matrix is secreted in senescent tumor cells (28, 43). It has also been noted that highly-expressed chemokine ligands (CCL) and C-X-C motif ligand (CXCL), can induce inflammation and chemoattract other cells, immune cells and non-senescent tumor cells (28, 57). Among the chemokines, CXCL12 is a chemokine that can lead to non-senescent tumor cells (28, 58). CXCL12 was not expressed in senescent fibroblasts due to hypermethylation of its promoter, however it was largely expressed in senescent tumor cells (28, 32). Furthermore, usually non-senescent tumor cells express a large amount of C-X-C chemokine receptor 4 (CXCR4). Senescent tumor cells secrete CXCL12 that was observed to be related to cancer cell migration and metastasis by interaction with non-senescent tumor cells (28). In addition, senescent tumor cells prevent anoikic cell death in lymphatic vessels, helping tumor cells survive and metastasize to target organs (28). This result suggests that senescent tumor cells are actively involved in cancer progression (28). Thus, senescent tumor cells are thought to play a role in suppressing cancer progression, and also have a role in promoting cancer progression (Fig. 1). Therefore, the study of senescent tumor cells in various organs should be continued.

As mentioned above, senescent tumor cells can be observed in primary cancer tissues (25-28), but they are also observed following anti-cancer treatment with chemotherapy or irradiation (18). Induction of senescent cells from cancer cells has been thought to be a reliable therapeutic strategy in tumor therapy (14). Cancer cell death is observed in lethal dose after administration of chemotherapy or radiation, but in cases where sub-lethal doses were given, senescent cells were found (14). Furthermore, the use of retinoic acid for the treatment of acute promyelocytic leukemia, and the resulting induction of

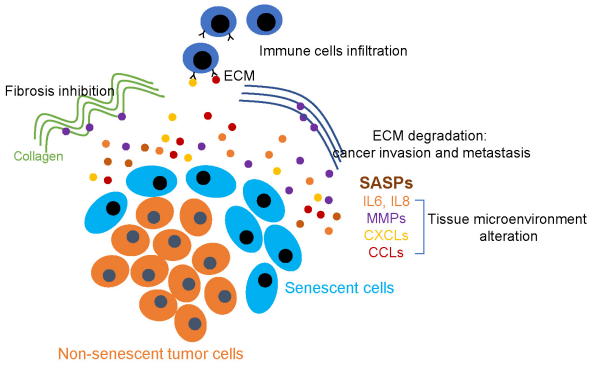

Fig. 1. Schematic representation of the role of senescent cells in tumors. Senescent cells express SASP and are involved in interactions with the tissue microenvironment, including extracellular matrix (ECM) degradation, immune cells infiltration, and cancer invasion.

senescent cells in the tumor by the cell dependent kinase 4 (CDK4) and CDK6 inhibitor palbociclib, can improve the patient's prognosis. This is called therapy induced senescence (14). However, as mentioned above, long term treatment seems to have a side effect with SASP expression. Therefore, the combination of senescence-inducing therapy with interventions that clear senescent cells could be beneficial to short- and long-term outcomes in cancer patients (18).

Little is known yet about the induction action mechanism of senescent tumor cells. Obviously, morphologically, they are malignant tumor cells that progress beyond the pre-cancerous stage. However, why senescent tumor cells are induced has not yet been elucidated. If reactive oxygen species (ROS) or hypoxic stress induces senescence (59), a large amount of senescent tumor cells should be observed in the central region of the tumor. The possibility of senescence induction by ROS seems low, however because senescence is observed in the peripheral region of tumors (28). Furthermore, we do not think it is a precancerous stage. As mentioned earlier, it is morphologically malignant tumor cells and involve cancer cells migration and metastasis which is characteristic of malignant tumor. Therefore, more studies should be performed in this field.

CONFLICTS OF INTEREST

The authors have no conflicting interests.

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