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SASP- NOVEL ROLE EXPLAINED - CHEMOTHERAPY, RADIOTHERAPY, IMMUNOTHERAPY, TARGETED THERAPY AND PREVENTION IN OBESITY ATHEROSCLEROSIS.

Oncology

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ABSTRACT

The purpose of the narration is to know the molecular mechanism, fibrosis, pleiotropic effects and co relation between Senescence-Associated Secretory Phenotype SASP , multitargeted role and immunostimulatory nature of SASP ,are modulated it for combating cancer other age -related diseases.

KEYWORDS

SASP, AGING, ATHEROSCLEROSIS, BIOMARKERS

INTRODUCTION

One promising tumour-prevention mechanism that prevents challenged or premalignant cancerous cells from replicating is cellular senescence. A vital process that exists to prevent tissues from destructive cell proliferation is cellular senescence, which additionally has a tumour-suppressive function. Apart from that after repetitive cell cycle in normal somatic cells coined as replicative senescence and seen in yeast, mammals in vivo. De oxy ribonucleoside (DNA) damaging results in associated stress-induced senescence. A malignancy has been defined by unrestrained proliferation of tumour cells and a greater frequency of somatic mutations than in healthy tissue. Senescence-Associated Secretory Phenotype (SASP), on the other hand, is associated with this steady proliferative arrest state. SASP is associated with the abundant release of proinflammatory signals within the tissue milieu and is, ironically, linked to age-related illnesses such as cancer. The aim of innovative treatments is to eradicate senescent cells through the utilization of senolytics or to eliminate the SASP without killing the senescent cell through utilizing what are known as "senomorphics." Additionally, fresh evidence suggests it is possible to modify the secretome's composition using pharmacological or genetic techniques.

Mechanism Of Senescence

Cellular senescence defines a phenotype and accompanied by a distinct secretory phenotype SASP produces a various of secreted proteins, cytokines, growth factors ,proteases and chemokines[1] ,the cyclin dependent kinase inhibitors p16 and p21 are induced by persistent DNA damage and in cancer also prevents the multiplication of cell harbouring the arrest of DNA and causes tumorigenesis but also influences the tissue microenvironment that helps in development of secretory phenotype[1-44]DNA damage occurred by the Ets family transcription factor by stabilizing p16.Irreversible cell cycle arrest is contributed by CDKIs P21 and P16, these are the compounds responsible for dephosphorylated from RB protein. In human cancer >50% the p53 and p16 are inactivated leads to senescence pathways are vital, high expression of p16 and p21 are more common and in vitro and in vivo. Various role of SASP in autocrine manner and paracrine manner, re enforcement of cellular senescence of senescent cells and inducing senescence cells in surrounding cells. Released chemokines from senescent cells as SASP factors acts on immune cell such as NK cells and macrophage acts as scavengers, SASP are capable of reprogramming of cells and repair of damaged cells.SASP explained in (Fig:1).[1,2,3,4,13,21,25,38,40]

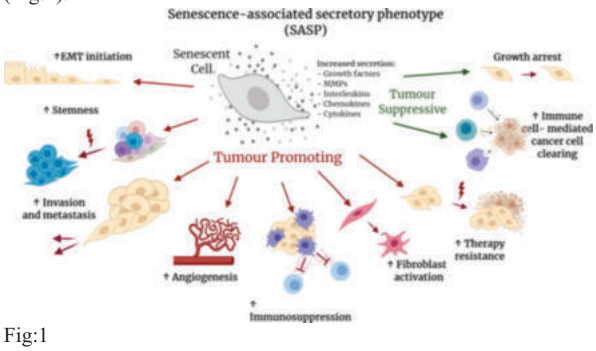


Fig:1

Physiological role of SASP is repairing of damaged tissue in vivo. Transient emergence of senescent cells with SASP in subcutaneous fibroblasts, damaged tissue cells reaffirm the immune cells that contribute to removal of damaged tissue. Fibroblasts produces growth factors as SASP promote the proliferation of skin progenitor cells to generate new skin .[9,28]

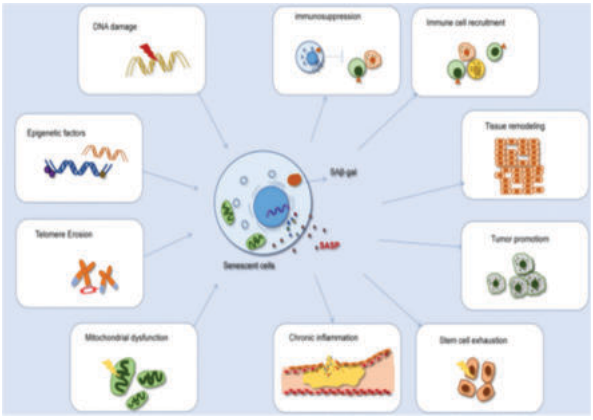
Liver injury where in hepatic stellate cells undergo cellular senescene to produce SASP factor and allow immune cells. Immune cells had a key role in eliminating senescent hepatic stellate cells to suppress the collagen production and prevent fibrosis. .[1,2,9,13,18,19,28]

Deleterious effects of SASP factors such as aging -associated inflammation and cancer are present. In several studies have reported

that cancer-associated fibroblasts (CAFs). The hepatic stellate cells identified in obesity associated liver tumour microenvironment undergo senescence and promotes tumour -promoting SASP factor production.(Fig; 1,2)(Table -1)[21,23,44]

Pathological SASP tendencies tends not to transient but to persist thereby inducing undesirable such as cancer progression or chronic inflammation, mechanism of SASP persists and essential for controlling SASP. (Fig 1,2)

SASP mechanism is explained and mechanism in cancer prevention, chemoprevention, cardiovascular disease neurogenerative disorders and cancer were explained. (fig:1,2)



The SASP role in tumorogensis,artherosclerosis ,fibrosis is explained Table -1 [9,28,35]

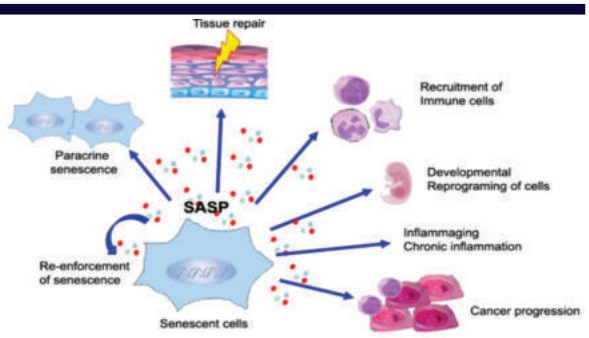
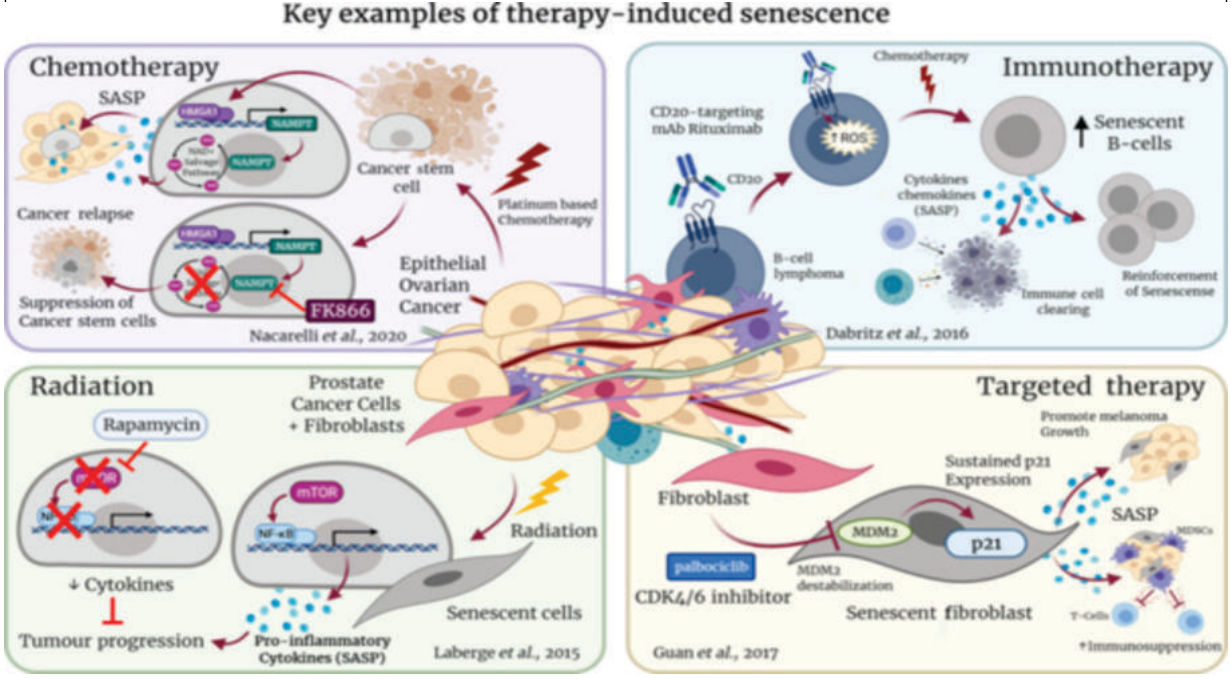


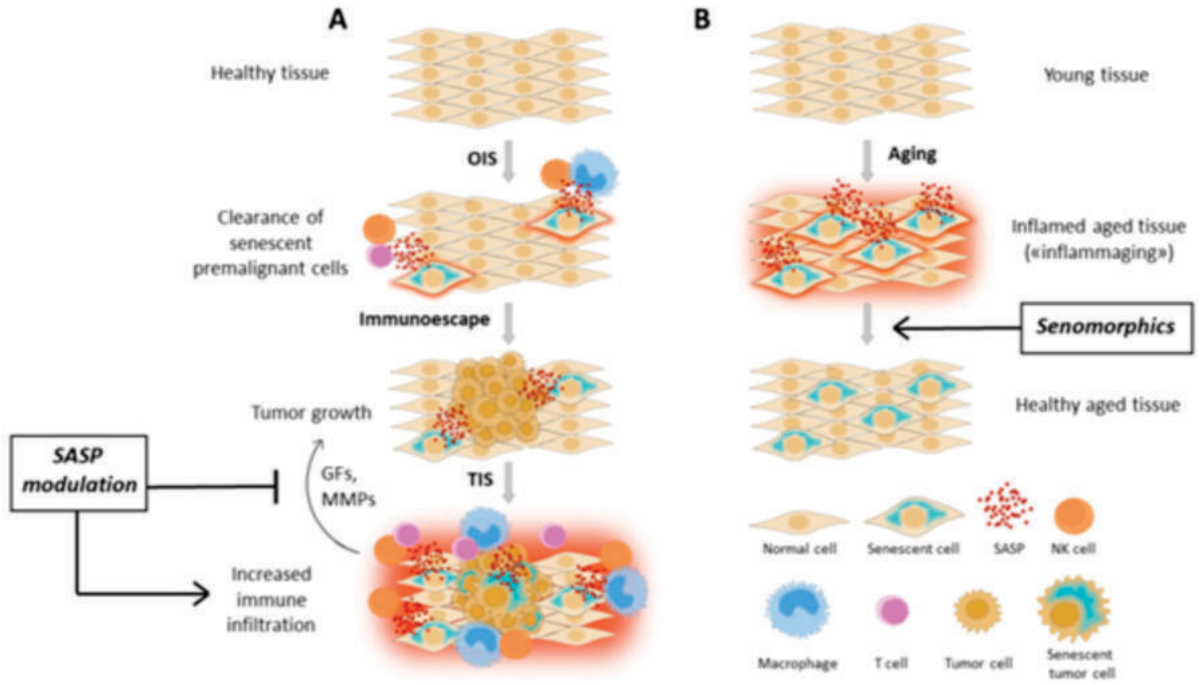
Fig :3 The effect of the SASP parameters. SASP factors possess the autocrine capacity to amplify cellular senescence. In addition, SASP factors may have a paracrine effect, causing the surrounding cells to senescitate (paracrine senescence). SASP factors aid in immune cell recruitment and healing of tissues. [1,2,13] Development can be influenced by SASP variables (developmental senescence). However, when they continue, SASP elements are linked to persistent chronic inflammation and the advancement of cancer.[1,2,5,13,21,26]

Hence forth, cancer can be avoided by eliminating precancerous senescent cells. Consequently, the senescence surveillance system is the term used to describe the senescent cell clearance system. The system's effectiveness was initially shown in a liver cancer model, where immune cells were recruited by SASP factors from precancerous senescent hepatocytes to eliminate precancerous cells. Therefore, it is crucial to eliminate senescent cells quickly and cancel SASP afterward to prevent the early beginning of cancer[18,19]

Senescence may arise from an array of cellular strains, including as oxidative stress, telomere or genomic impairment, epigenomic issues, and modifications to oncogenic or tumour suppressor expression . These treatments have an opportunity to activate the retinoblastoma (Rb) and p53 tumor suppressor pathways, which in turn might result in enhanced expression of p16INK4A and cell cycle arrest. Subsequent activation of multiple downstream pathways linked to DNA damage, cell cycle arrest, and inflammation can result in the induction of SASP in these cells.produces inflammatory cytokines such as IL-1a, IL-1b, IL-6, IL-8, IL-18, CCL-2, tumour necrosis factor (TNF-a), metalloproteases (MMP-1, -3, -8, -9, -13), and many growth factors, including vascular endothelial growth factor (VEGF), PDGF-AA [1,2,5,12,13,20,21,23,25,28,33,38,44]	
ATM	CHK2
p38 MAPK	CCAAT/enhancer-binding proteins (C/EBP)
NFκB mTOR and JAK-STAT signalling	Faget, Ren
Growth factors (vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), hepatocyte growth factor (HGF)), interleukins (IL-1α, IL-6, IL-8, IL-10, IL-13, IL-15),[21 23 244] matrix metalloproteinases (MMP3, MMP9) and cytokines/chemokines (CXCL1, CXCL2, CXCL5, CXCL11, CXCL12, CCL2, CCL20)-non of them were no single phenotype.[36,37]	
CHEMOTHERAPY ,RADIOTHERAPY,IMMUNOTHERAPY,TARGETED THERAPY induce the SASP- catastrophic DNA damage, leading to a DDR, which can cause subsequent senescence and associated SASP. For instance, Logue et al. (2018) found that paclitaxel, a typical drug used to treat triple-negative breast cancer (TNBC), increases the activity of the enzyme inositol-requiring enzyme 1 alpha (IRE1) RNAse, which results in abnormal suppression of ER stress. Improvements in SASP-associated factors such IL-6, IL-8, CXCL1, granulocyte-macrophage colony-stimulating factor (GM-CSF), and TGFβ2 are caused by this increase in IRE1 activity.[6,16,17]	

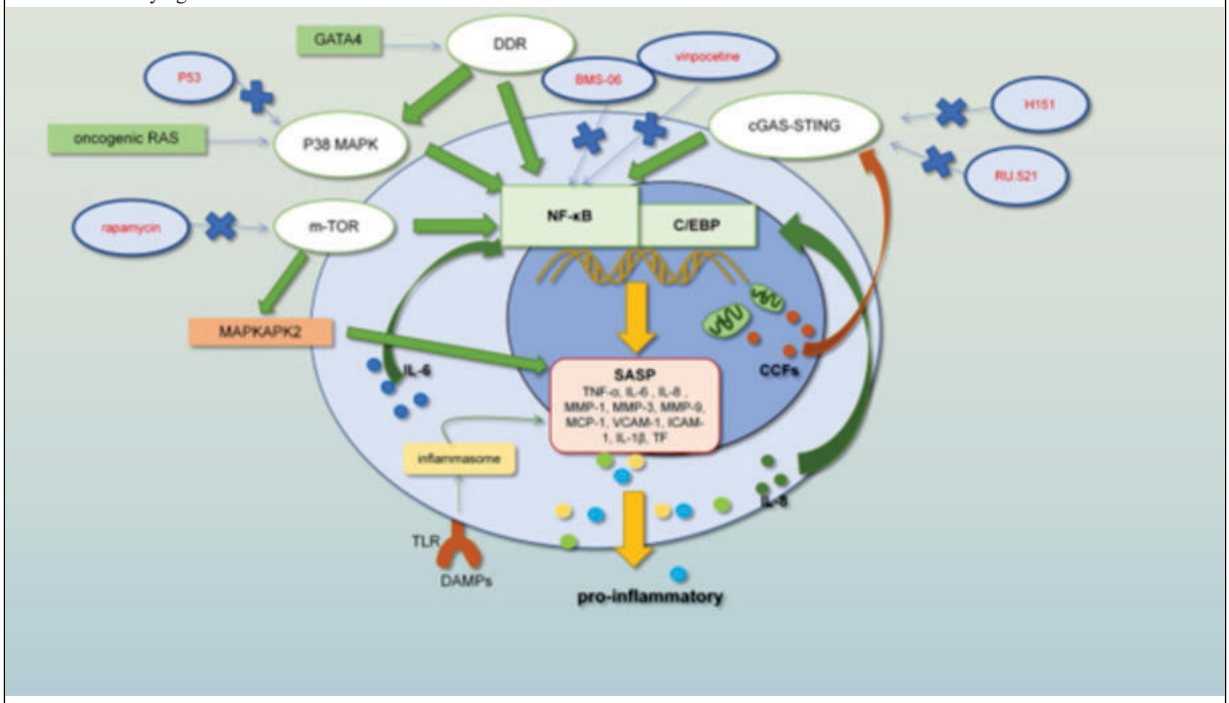


Therapeutic approach



• strong correlation between DNA damage-induced senescence and NF-κB-regulated SASP. Regulatory mechanism of SASP[61617]

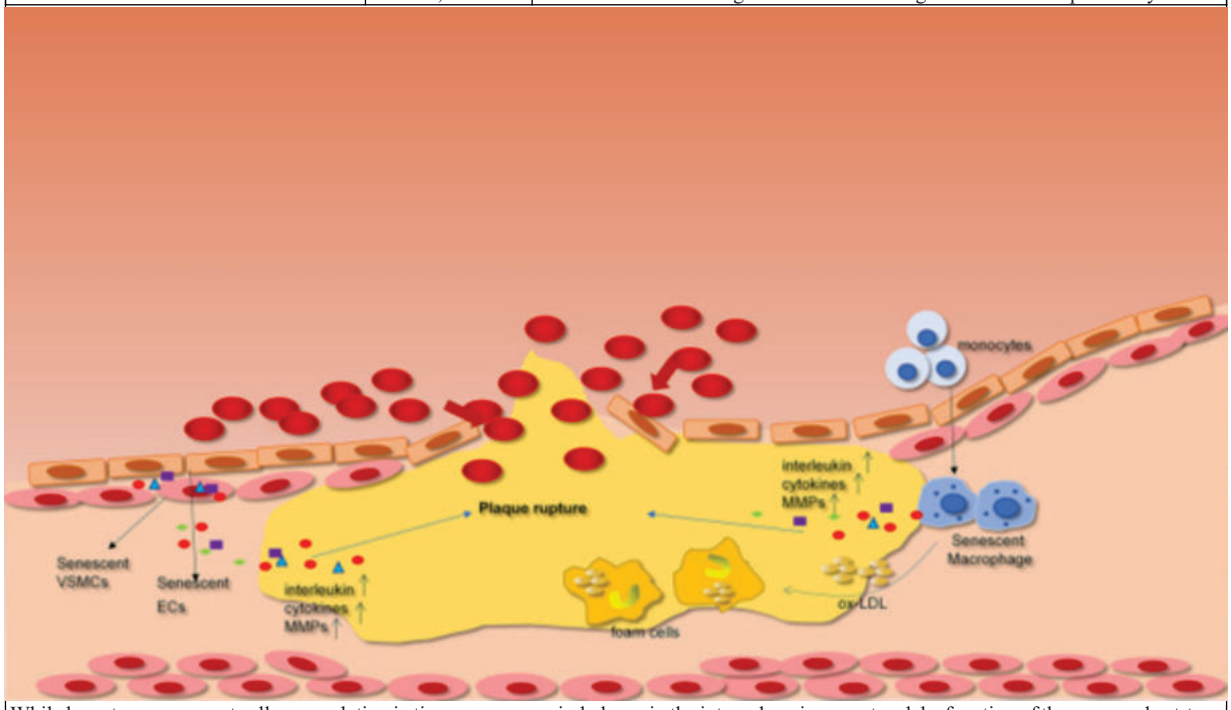
• Several cellular regulatory factors such as p38MAPK, Jak2/Stat3, inflammasomes, m-TOR, miRNA, GATA-4, macroH2A1 and ATM have been proven to play roles during the generation of SASP. It is worth noting that the regulation of the SASP appears to be centred on the NF-kB complex and C/EBP family.fig 4[1-44]



EFFECT OF SASP ON ATHEROSCLEROSIS(FIG 5)

ell type	SASP	Effect on atherosclerosis
Senescent endthelial cell	IL-6	Form atherosclerotic plaques and cause thrombosis
	IL-1	Recruit more immune cells and form atherosclerotic plaques
	IL-8	Form atherosclerotic plaques and cause thrombosis
	IL-15	Form atherosclerotic plaques
	MCP-1	Recruit more immune cells and form atherosclerotic plaques
	TNF	Recruit more immune cells and form atherosclerotic plaques
	ICAM-1,VCAM-1	Recruit circulating monocytes and vascular injury
	ET-1	Vascular endothelial dysfunction
	PAI-1	Cause thrombosis
	VEGF	Promote plaque angiogenesis and vascular remodeling

Senescent vascular smooth muscle cell	IL-1α	Leading to inflammation and monocyte chemotaxis, and proteolysis
	IL-6	Leading to inflammation and impaired vascular mitochondrial function
	IL-8	Induce angiogenesis in coronary plaques
	CCL-3, 4	Recruit monocyte/macrophage cells and increase plaque size
	MCP-1	Recruit monocyte cells
	TGF-β1	Enhance arterial stiffness and initiate the senescence of other cells
	MMP-1,2,3,7,8,9, 10,12,13,14	Fibrous cap of the plaque becomes thinner and extracellular matrix degradation
	OPG	Vascular calcification;
	VEGF	Promote plaque angiogenesis and vascular remodeling
Senescent T cell	IL-6	Leading to inflammation
	TNF-α	Leading to inflammation
	IFN-γ	Induces the activation of macrophages
Senescent macrophage	IL-1β	Leading to inflammation
	IL-6	Leading to inflammation
	TNF-α	Leading to inflammation
	MMP-3, 13	Extracellular matrix degradation and thinning of the fibrous cap in artery



While long-term senescent cell accumulation in tissues causes an imbalance in the internal environment and dysfunction of the organs, short-term senescent cell accumulation in tissues is crucial to the stability of the internal environment and organ function.

REVERSE EFFECT IS DIE TO SASP.[5,7]
SENOLYTICS AND SENOSTATICS: TARGETING AND UTILISING THE SASP

Senolytics		
	BLC□2 inhibitor	↓ HCC tumour growth following FBP1 loss via SASP inhibition [
		↓ PARP inhibitor induced senescent cells in ovarian and breast cancer
		↓ Metastatic burden by targeting TIMP1□deficient senescent cells in prostate cancer
GX15-070 (Obatoclax)	BCL-2 inhibitor	↑ Apoptosis of senescent cells induced by BET inhibition in TNBC
		↓ Senescent cells induced by BMI1 inhibition enhancing tumour killing in DIPG
uPAR CAR T cells	uPAR	↓ Senescent cells extending lung adenocarcinoma survival.
Senostatics		
Dasatinib	SRC-family protein-tyrosine kinase inhibitor	↓ HCC tumour growth following FBP1 loss via SASP inhibition
FK866/GMX1778	NAMPT inhibitor	↓ Senescent-associated cancer stem cell outgrowth in EOC
Irinotecan	TOP1 inhibitor	↑ SASP in ovarian cancer sensitising cells to anti-PD-1 therapy
Metformin	Gluconeogenesis inhibition	↓ mTOR and STAT3 pathway signalling in response to a CDK4/6 inhibitor repressing the stemness of HNSCC cancer cells.
NVP□BSK805	JAK2 inhibitor	↓ SASP in Pten-deficient prostate tumours leading to increased CD8 activity
Rapamycin	mTOR inhibitor	↓ Senescent fibroblasts in prostate cancer inhibiting tumour growth
Sertraline	Serotonin reuptake inhibitor	↓ mTOR signalling in HCC senescent cells causing apoptosis and reduction of tumour growth
Y-27632	ROCK inhibitor	↓ IL-6 and IL-8 production from senescent oral keratinocytes

CONCLUSION

SASP had the efficacy in treating cancer obesity age related diseases and atherosclerosis. A hidden marker and the function ,drugs to used wisely to be know in treating cancer .SASP plays a major role .Tumour microenvironment further studies to be focused to improve the expectancy in patients.

Abbrevations

cancer-associated fibroblasts CAFs
De oxy ribonucleoside DNA
SASPSenescence-associated secretory phenotype
CVDCardiovascular disease
LDLLow-density lipoprotein
SaβG Senescence-associated beta galactosidase
VEGF Vascular endothelial growth factor
PDGF Platelet derived growth factor
MMPs Metalloproteases
EV Extracellular vesicle
TNF Tumor necrosis factor
ECM Extracellular matrix
DAMPs Damage-associated molecular patterns
M-TOR Mammalian target of rapamycin
DDR DNA damage reaction

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