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REVIEW

Tumor-Associated Senescent Macrophages, Their Markers, and Their Role in Tumor Microenvironment

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Abstract—Tumor-associated macrophages (TAMs) are an important component of the tumor microenvironment (TME) and the most abundant population of immune cells infiltrating a tumor. TAMs can largely determine direction of anti-tumor immune response by promoting it or, conversely, contribute to formation of an immunosuppressive TME that allows tumors to evade immune control. Through interactions with tumor cells or other cells in the microenvironment and, as a result of action of anti-cancer therapy, macrophages can enter senescence. In this review, we have attempted to summarize information available in the literature on the role of senescent macrophages in tumors. With the recent development of senolytic therapeutic strategies aimed at removing senescent cells from an organism, it seems important to discuss functions of the senescent macrophages and potential role of the senolytic drugs in reprogramming TAMs to enhance anti-tumor immune response and improve efficacy of cancer treatment.

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INTRODUCTION

Tumor microenvironment (TME) comprises a complex heterogenous system including immune cells, endothelial and stromal cells, as well as extracellular matrix [1-7]. Recent analysis of single-cell transcriptome (single-cell analysis, SCA) demonstrated that up to 90% of cells in the tumor microenvironment could be non-transformed [8]. TME composition varies depending on the type and stage of the tumor development; organ in which a primary tumor emerges; factors expressed by the tumor cells, and patient's anamnesis [9].

Recently more attention has been paid to the effects of cell aging, or the so-called senescence state on the tumor growth and development [10]. Phenotype of senescent cell is heterogenous and depends on the type of the cells subjected to senescence and factors causing this state. In general, senescence is defined by the irreversible arrest of cell cycle, elevated lysosomal activity, resistance to apoptotic stimuli, enhanced glycolysis, increased DNA damage, as well as by the increased secretion of chemokines, cytokines, and growth factors combined under the name senescence-associated secretory phenotype (SASP). Through the paracrine effects on the surrounding cells, SASP could facilitate

Abbreviations: Arg1, arginase; BMDM, bone marrow-derived macrophages; LCCM-BMDM, bone marrow-derived macrophages cultivated in L929-cell conditioned medium; M-CSF-BMDM, bone marrow-derived macrophages cultivated with recombinant M-CSF; NAD, nicotinamide adenine dinucleotide; SCA, single-cell analysis; TME, tumor microenvironment; SASP, senescence-associated secretory phenotype; TAMs, Tumor-associated macrophages; TGF-β, transforming growth factor beta.

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initiation of epithelial-mesenchymal transition [11, 12], acquiring pluripotency (stemness) by the cells [13, 14], local tissue invasion [15], angiogenesis [16], fibroblast activation [17], immunosuppression [18, 19], enhanced metastasizing [20], and resistance to therapy [21].

Based on the above-mentioned functions, identification of the senescent cells most often is based on such markers as enhanced expression of cell cycle inhibitors, $p16^{INK4}$ and $p21^{cip1}$ [22]; increased activity of lysosomal β-galactosidase associated with aging [23]; increased content, in comparison with other cells, of the phosphorylated form of H2AX histone reflecting presence of DNA damage; cytokines typical of SASP, such as, IL-6 [24]. It must be mentioned that at present there is no unique single marker of senescence, and most often several methods are used to confirm this cell phenotype.

In addition to spontaneous aging, the therapy-induced aging is often detected in TME. It was shown in various studies that the classic cytotoxic therapy, targeted therapy, and immunotherapy could induce cell aging [25]. Under the action of these factors all cell types in TME could be subjected to senescence and affect tumor cells. However, the tumor-associated macrophages (TAMs), which play an important role in TME comprising the most prevalent population of immune cells infiltrating tumor, attract most attention in the context of senescence [26]. As immune system cells, they define, to a large extent, immune landscape of the TME, and could facilitate the disease progression [8]. In particular, it was shown that the presence of TAMs in a tumor is associated with poor prognosis of the disease and low efficiency of therapy [27-29]. Despite the fact that removal or reprogramming of senescent TAMs seems as a promising approach to increase efficiency of cancer therapy, up to recent times information on the phenotype typical for the senescent macrophages in TME and mechanism underlying its formation was practically absent. Hence, it seems reasonable to discuss progress in the area of research associated with the active search for universal biomarkers of the senescent TAMs and with the recently introduced novel models for detection of biological effects of this cell subpopulation on the tumor growth and development.

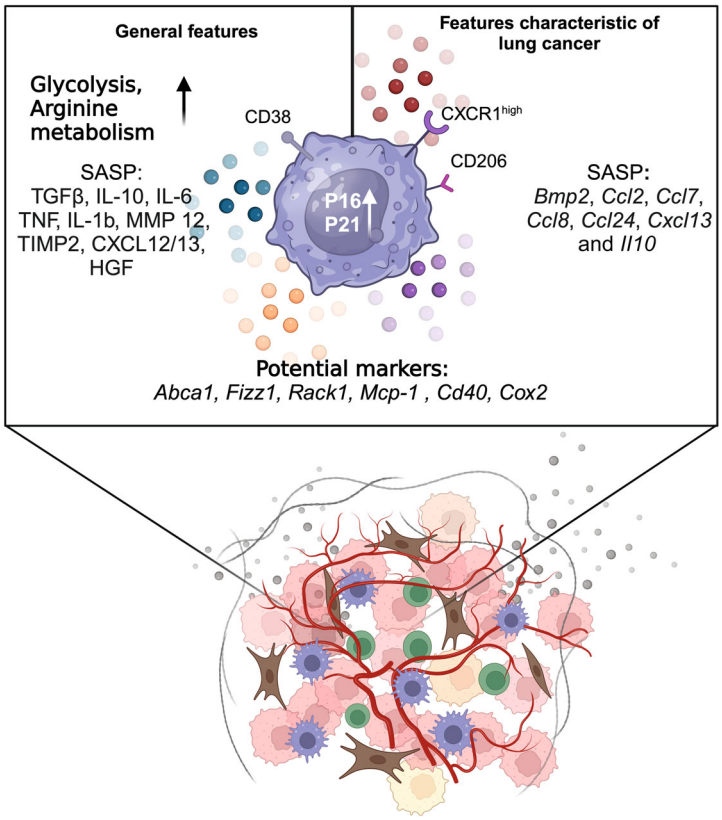
SENESCENT MACROPHAGES IN A TUMOR

Same as other types of cells in tumor microenvironment, TAMs could be subjected to senescence, however, potential biological mechanisms of appearance of senescent macrophages in a tumor and their prognostic value are poorly understood [28]. The fact that the *in vivo* and *in vitro* phenotypes of the macrophages from the same type of tumor could differ significantly complicates investigation of this issue. Moreover, the heterogeneity of the mechanisms and pleiotropy of the senescence mediators in tumor diseases is further complicated by the genetic diversity of human tumors and complex interactions between the tumor cells and cells in their microenvironment during oncogenesis [30]. At the same time, cells in TME could also have a very heterogenous phenotype. In particular, macrophages *in vivo* are characterized by the wide spectrum of subpopulations, in which subpopulation of senescent macrophages seems to be therapeutically significant. The features of senescent macrophages allowing to distinguish them from other subpopulations of macrophages will be described below (figure).

Phenotype of senescent TAMs. To date the following subpopulations of TAMs have been described the most: proinflammatory M1-like and immunosuppressive M2-like macrophages [more detailed description of M1 and M2 macrophages are provided in the paper by Yurakova et al. [31] in this issue of Biochemistry (Moscow) journal]. Phenotype of the senescent macrophages in the tumor microenvironment could be assigned neither to the traditional polarization classes typical for M2 (high expression of *Arg1*), nor typical for M1 (high expression of *iNOS*). Macrophages in TME could have different phenotypes depending of the tumor type, nature of therapy, and particular clinical manifestations [32]. Hence, search for the specific markers allowing selective distinguishing of the senescent macrophages from the other TAMs is an important task for the development of therapy targeting this population of the cells. Available data and identified markers typical for the senescent and M1/M2 macrophages are summarized and compared in Table 1 [33].

Aging is accompanied by chronic inflammation, which is manifested by the increase of expression of SASP components: proinflammatory cytokines IL-1α, IL-6, and TNF, C-reactive protein, matrix metalloproteases MMP-3 and MMP-9 modulating extracellular matrix, as well as chemokines CXCL-1 and CXCL-10 attracting neutrophils and monocytes, respectively [46, 54]. All these factors could affect tumor cells and their environment. It was concluded in the recent meta-review by Moss et al. that the markers of proinflammatory (M1) macrophages including CD11c, iNOS, MHC-II, and CD80 commonly increase with age [55]; however, it is still unknown how this is associated with the pattern of tumor microenvironment.

Another part of the data is concentrated on the fact that the senescent macrophages have a M2-like phenotype. It is generally recognized that the macrophages with M2-polarization demonstrate enhanced expression of arginase-1 (Arg1) involved in arginine metabolism [33], and facilitate development of the non-small-cell lung cancer, and their presence in a tumor microenvironment correlates with lower survival of the patients, increased metastasizing, and enhanced



Potential markers of senescent TAMs. More universal markers found in different models of tumor genesis are shown on the left; and characterized TAMs from the lung tumors are shown on the right. Combined increase of the expression of inhibitors of cyclin-dependent kinases $p16^{INK4}$ and/or $p21^{cip1}$, Arg1, CD206, CXCR1, CD38 is typical for the senescent TAMs, as well as increased arginine metabolism and glycolysis. SASP of the senescent TAMs is characterized by secreted molecules such as TGF-β, IL-10, IL-6, TNF, IL-1β, MMP12, TIMP2, CXCL12, CXCL13, HGF. For the lung cancer models the following molecules secreted by the TAMs were detected: *Bmp2*, *Ccl2*, *Ccl7*, *Ccl8*, *Ccl24*, *Cxcl13*, and *Il10*. The markers *Abca1*, *Fizz1*, *Rack1*, *Mcp-1*, *Cd40*, *Cox2* have been less investigated, but have certain diagnostics potential for identification of senescent macrophages. Created with the help of BioRender.com.

Table 1. Comparison of the markers typical for M1/M2 and senescent macrophages

Markers	M1 [34-37]	M2a [8, 34, 37, 38]	M2b [38, 39]	M2c [38, 40]	M2d [38, 41-43]	Senescent macrophages [8, 44-53]
TNF, IL-6	+	–	+	–	–	+
IL-10	–	+	+	+	+	+
TGF-β	–	+	–	+	–	+
IL-1	+	–	+	–	–	+
CD206	–	+	–	–	–	+
ARG1	–	+	–	+	+	+
iNOS	+	+	–	–	+	+/–
MHC-II, CD80	+	–	–	–	–	+/–
CD163	–	+	+	–	–	+
CD38	+	–	–	–	–	+
Expression of Toll-like receptors (TLRs)	TLR2/4	–	–	TLR1/8	–	expression of all TLRs decreases

proliferation of tumor cells [56, 57]. Moreover, the aging TAMs also exhibit the M2-like immunosuppressive phenotype, which was demonstrated in several studies [8, 34, 37-43]. Gene clusters expressed in the senescent macrophages from the samples derived from the patients with refractory bladder cancer were identified using single-cell transcriptome analysis [27]. Among those genes, the gene of transforming growth factor beta (*TGF-β*) was detected, which is characteristic for the immunosuppressive tumor microenvironment. Expression of the aldo-keto reductase B gene (*AKR1B1*) was also noted, which plays an important role in inflammation and metabolism of various chemotherapy preparation, as well as in cell differentiation, proliferation, and apoptosis [28, 58].

Both in humans and in mice the senescent TAMs demonstrate reduced expression of the molecules of major histocompatibility complex (MHCII) and of the Toll-like receptors (TLR) [52], which is accompanied by the decrease of phagocytic activity [59], efferocytosis, and autophagy [46]. This also characterizes the aging macrophages as more immunosuppressive cells despite the enhanced expression of SASP.

New potential markers of the senescent macrophages (ABCA1, FIZZ1, RACK1, MCP-1, CD40, COX2) reported in the recent systematic review by Moss et al. [55] should be also mentioned. It is likely that these markers also play an important role in the senescence of TAMs. Despite the fact that there is no unique marker identifying aging cells, overexpression of the cyclin-dependent kinases $p16^{INK4a}$ and $p21^{cip1}$ has been used for a long time as a marker of aging cells *in vitro* and *in vivo* both in mouse and human models [48, 60, 61] including for macrophages [49, 50, 62].

Metabolism of senescent TAMs. In addition to phenotypic characteristics, functional and metabolic features of the senescent macrophages also should be considered. One of the peculiarities of the senescent cells is preservation of metabolic activity supporting SASP program and other specific functions despite the arrest of cell cycle [63]. As a rule, accumulation of dysfunctional mitochondria occurs in the senescent immune calls, as well as activation of glycolysis instead of oxidative phosphorylation (OXPHOS), which leads to bioenergetic imbalance [64].

Similar metabolic adaptations are typical for the proinflammatory M1 macrophages, which predominately use glycolysis and demonstrate reduced OXPHOS, while the alternatively activated M2 macrophages depend mostly on OXPHOS [65, 66]. From the functional point of view enhanced glucose metabolism in TAMs is required for synthesis of various molecules involved in SASP, in particular, it facilitates enhanced secretion of cathepsin-B by macrophages and tumor progression [63, 67, 68]. Interestingly enough, metabolic adaptations of other types of senescent cells could be different from the adaptations in the senescent TAMs. For example, increase of oxidative phosphorylation is typical for the senescent endothelial cells [69], hepatocytes [70, 71], β-cells in diabetes [72, 73], and hematopoietic stem cells [74]. However, increase of glycolysis is more typical for the senescent macrophages. Inhibition of this metabolic pathway could potentially be an approach for senolytic therapy [75].

Nicotinamide adenine dinucleotide (NAD) is present in an organism in an oxidized (NAD^+) and reduced state (NADH). NAD is an important coenzyme for redox reactions, which plays one of the key roles in the energy metabolism [76], and also is a substrate for sirtuins, PARP1, and ectoenzymes CD38 and CD157 [77]. Numerous studies have shown that NAD^+ levels decrease with age [78]. It has also been shown that the monocytes and macrophages of elderly patients have reduced respiratory capacity due to insufficient level of NAD [64].

Activation of CD38 during aging could lead to increased signalling by NF-κB in macrophages [53, 79], which facilitates induction of the SASP factors expression [80]. The SASP factors, such as IL-6 secreted in the tumor microenvironment, could activate the expression of CD38 in macrophages [63]. The ectoenzymes CD38 and CD157, in turn, can hydrolyse NAD^+ in tumour tissues and release extracellular adenosine, which is involved in immunosuppression [81]. Hence, aging cells expressing CD38 could initiate loss of NAD^+, which could lead to an increase of the number of senescent cells through the effects of SASP factors via the positive feedback mechanism.

The NF-κB signaling and the level of mitochondrial Ca^{2+} (mCa^{2+}) play an important role in regulation of inflammatory response, induction of the SASP phenotype, and polarization of macrophages [82]. Association between the NF-κB signaling and calcium metabolism was observed during analysis of 700 human transcriptomes. This analysis revealed that age correlates with the expression of the mitochondrial calcium uniporter gene (*MCU*) and its regulatory subunit *MICU1*. These genes play an important role in the transmission of mCa^{2+} signals [47].

EFFECTS OF SENESCENT TAMs ON TUMOR PROGRESSION

Pathogenic effects of senescent macrophages on growth and development of tumors in the non-small cell lung cancer models were demonstrated in the recent year. Haston et al. established a mouse model, p16-FDR, which allowed to establish that TAMs and, to a lesser degree, endothelial cells comprise the main pool of senescent cells populating the KRAS-induced lung tumors [8]. Removal of the $p16^{INK4a+}$ senescent

Table 2. Main senolytics currently used

Senolytic/Senomorphic	Mechanism of action	Effect on senescent macrophages	References
Dasatinib + Quercetin	inhibition of Src/Abl HIF-1α, PI3-kinase	exerts effects	[84, 85]
ABT-263 (Navitoclax)	inhibition of proteins of Bcl-2 family	exerts effects	[86]
ABT-737	inhibition of proteins of Bcl-2 family	exerts effects	[8]
Venetoclax	proteins of Bcl-2 family	not investigated	[87]
Fisetin	PTEN-mTor cascade	exerts effects	[88]
SR12343	inhibitor of NF-Kb	not investigated	[89, 90]
Apigenin	IRAK1/IκBα/NF-κB	not investigated	[91, 92]
Cardiac glycosides	mainly inhibitors of Na^+/K^+-ATPase	not investigated	[93-95]

cells using senolytic approaches was shown to prolong survival and inhibit tumor growth [8, 83]. Senescent TAMs in the p16-FDR model demonstrated the $CD206^+p16^{INK4a+}$ phenotype and also expressed numerous tumor-stimulating SASP factors, which were found to be unique to the tumors formed in the lungs (*Bmp2*, *Ccl2*, *Ccl7*, *Ccl8*, *Ccl24*, *Cxcl13*, and *Il10*), and not typical for the previously described classic SASP factors such as *Tnf*, *Mcp1*, *Il6*, *Il1b Il7*, *Mmp12*, *Timp2*, *Cxcl-12/13*, *Hgf*) [8, 50, 51]. The study by Haston et al. [8] became a key study in the field of senescent macrophages in tumors, as there was no clear understanding of whether the macrophages actually had senescent cells properties. Interestingly enough, the macrophage phenotype similar to that one observed in the KRAS-induced lung tumors in mice was also found in the old mice at the age of 20-22 months.

A previously established transgenic mouse line (INK-ATTAC) [29] was used in the study by Prieto et al. Using SCA, the authors found with the help of SCA a population of senescent alveolar macrophages $SIGLEC^+p16^{INK4a+}CXCR1^{high}$ localized in the tissues of old mice and in lung tumors. The $SIGLEC^+p16^{INK4a+}CXCR1^{high}$ subpopulation promoted adenoma formation and inhibited proliferation and tumor infiltration with the $CD8^+$ lymphocytes. Targeted depletion of the $p16^{INK4a+}$ senescent cells in the INK-ATTAC model prevented development of negative effects mediated by the senescent cells in TME, and slowed down oncogenesis in the KRAS mice [29].

The studies by Prieto et al. [29] and Haston et al. [8] show that the strategy involving removal of senescent macrophages from the TME has an anti-tumor potential. This approach could be suggested as an adjuvant therapy for treatment of oncological diseases.

A new class of drugs, the senolytics have been suggested as agents for selective removal of senescent cells. Information on the most popular and widely used senolytics is presented in Table 2. Some of them have already been approved for clinical use in the treatment of various diseases, hence, so their repurposing for senolytic therapy could occur within a short period of time, and such preparations might be used for reprogramming of tumor microenvironment in the cancer patients in the nearest future.

VARIETY OF MODELS FOR INVESTIGATION OF SENESCENT TAMs

In the final section of the review, we consider important to summarize existing approaches to modeling of TAMs and discuss whether some of the models could be used to model senescent TAMs. In particular, the following *in vitro* approaches have been suggested in the literature: association of the primary macrophages or cell lines with the tumor adding tumor-cell conditioned medium [96], co-cultivation, cultivation in a Transwell® system [33, 97], isolation of TAMs directly from tumor tissues and their following *in vitro* cultivation [98-100].

Human TAMs *in vitro*. The most popular approach is based on the use of transformed human monocytic cell lines such as THP-1 and U937 after stimulation with phorbol-myristate-acetate. The obtained macrophages are cultivated in a tumor-cell conditioned medium [101], in some cases factors facilitating development of the M2-like phenotype (IL-4 and IL-10) are added [102]. This approach helps with the model standardization; however, this approach has several

drawbacks for investigation of senescent TAMs such as initial priming of the cells in the direction of the M2-like phenotype, which limits the possibilities for monitoring changes in the transcription and metabolic profiles in this particular model in response to association with tumor and following induction of aging.

Another method for creation of human TAMs is based on obtaining macrophage precursors from the human peripheral blood by cultivation in the presence of human granulocyte-macrophage colony-stimulating factor (GM-CSF) followed by activation with IFN-g, LPS for M1, while for obtaining of M2 and TAMs macrophages are differentiated in the medium containing human macrophage colony-stimulating factor (M-CSF) followed by stimulation with IL-4 [103].

It is worth noting that the 2D *in vitro* system, in which TAMs are prepared by adding tumor-cell conditioned medium directly to macrophages, is often insufficient to detect changes associated with the senescent macrophages. In particular, only co-cultivation of macrophages with tumor cells in the study by Enukashvily et al. [104] allowed detecting transcription of pericentromeric satellite repeats HS2/HS3, which are likely to be associated with aging. These differences demonstrate importance of direct intercellular interactions between the cells of microenvironment and tumor cells, which is also important to consider during selection of the model of TAMs.

Mouse TAMs *in vitro*. It is our opinion that the *in vitro* models of human and mice TAMs have a number of fundamental differences. In particular, the main approach to generate mouse TAMs *in vitro* is based on the use of bone marrow-derived macrophages (BMDM). Two possible methods of macrophage differentiation for modelling mouse TAMs have been described for mouse TAMs modeling in the literature: (i) by addition of mouse M-CSF (M-CSF-BMDM); (ii) by addition of a medium conditioned by the L929 (LCCM) cell line (LCCM-BMDM) [31]. In addition to M-CSF, LCCM contains chemerin (Rarres2), factor inhibiting migration of macrophages (Mif), osteopontin, Ccl7, Ccl2, Cxcl1, Cx3cl1, Ccl9, Gerem1, and Tgf-β [105]. Macrophages generated by these two methods differ in a number of parameters, which has been described previously; the differences were observed both in the case of stimulation with LPS and in the non-activated state. The LCCM-BMDM secrete Tnf, Il-6, and Il-12 at lower levels after LPS stimulation compared to the M-CSF-BMDM, show increase of glycolysis indicators, have larger mitochondrial mass with high percent of dysfunctional mitochondria. Secretion of Il-10 by the non-activated LCCM-BMDM has been demonstrated in comparison to M-CSF-BMDM [106]. This has to be taken in consideration when working with the senescent TAMs models *in vitro*, as the increase of the *Il10* expression in macrophages in the course of inflammatory processes has been described as one of the changes associated with aging [55].

The models investigating interactions of TAMs with tumor microenvironment *in vitro* provide several clear advantages despite being artificial to a certain degree. In particular, this approach enables less labor-consuming experimental design, is low-cost, and provides the possibility to perform high throughput screening of large libraries of chemical compounds with the goal of identification of novel medicinal preparations allowing to decrease negative properties of TAMs and to increase their anti-tumor activity.

In recent years investigations of tumor microenvironment using cultivation of tumor organoids have been actively developing. This approach occupies an intermediate position between the studies of the role of TAMs *in vitro* and *in vivo*; while this approach remains relatively simple and cost-effective, it allows effective modeling of complex three-dimensional interactions of TAMs with extracellular matrix and various types of cells in TME [107]. Considering rapid progress in this area, it could be expected that the experimental protocols involving cultivation of organoids will become very popular in the nearest future.

Study of TAMs *in vivo*. Experimental laboratory animal models of oncogenesis using predominantly mouse models remain the gold standard for the study of TAMs. Supplemented with success in single-cell sequencing (single-cell analysis, SCA) and SCA data on different signatures of TAMs derived *ex vivo* from the biopsies of cancer patients, this approach allows receiving most accurate results and expand our knowledge on the role of macrophages at different stages of oncogenesis [108-111]. In the section devoted to the effects of senescent TAMs on tumor progression, successful examples of creating and using *in vivo* models to study senescent TAMs have been presented [29]. Data on characteristics of these mouse models and a number of other promising *in vivo* models for the study of senescence are summarized in Table 3. Information presented in the Table 3 could help the interested researchers with selection of an appropriate experimental model [8, 29, 48, 62, 98-100, 112, 113].

CONCLUSIONS

Acquiring senescent phenotype by the cells of tumor environment including TAMs could significantly affect tumor progression and its resistance to modern anti-tumor therapies. Senescent modality of TAMs does not totally fit to the presently existing functional classification of macrophages such as M1/M2 polarization. Number of studies devoted to analysis of tumor microenvironment at the level of single cells is increasing exponentially; furthermore, novel and

Table 3. Mouse models for investigating senescence

Name of the mouse model	Description	Reporter system (color of senescent cells)	System for removal of senescent cells	Inducibility of the system	References
p16-3MR	*BAC* transgene; reporter cassette under control of $p16^{INK4a}$ promoter	luciferase/mRFP (red, ex584/em607)	HSV-TK + + ganciclovir	only cell removal – ganciclovir	[114]
p16-Cre and p16-CREERt2	knock-in of the cassette into the last exon $p16^{INK4a}$ after STOP codon	Rosa26-mTmG (green, ex484/em510)	Rosa26-lsl-DTA	Tamoxifen for p16-CREERt2	[62]
p16Ink4a-CreERT2	knock-in of the *CreERT2* gene into the first exon of $p16^{INK4a}$	Rosa26-CAG-lsl-tdTomato (orange, ex554/em581)	Rosa26-SA-lsl-DTR-IRES-tdTomato	Tamoxifen; Tamoxifen + + diphtheria toxin	[115]
p21-Cre	*attP* transgene; reporter cassette under control of the minimal promoter $p21^{cip1}$ p21-CreERT2-IRES-GFP	Rosa26-CAG-lsl-tdTomato (orange, ex554/em581); or (green, ex484/em510)	Rosa26-lsl-LUC/ Rosa26-lsl-DTA	Tamoxifen	[48]
INK-ATTAC	transgene; reporter cassette under control of the minimal promoter $p16^{INK4a}$	FKBP–Casp8-IRES-EGFP (green, ex488/em507)	FKBP–Casp8	only cell removal – AP20187	[29, 116]
p16-FDR	knock-in of the cassette into the last exon $p16^{INK4a}$ after the STOP codon; P16-P2A-FLPo-P2A-DTR-mCherry	Rosa26 frt-STOP-frt-EGFP (green, ex488/em507) or DTR-mCherry (red, ex587/em610)	DTR-mCherry	only cell removal – diphtheria toxin	[8]

Note. *HSV-TK*, herpes simple virus thymidine kinase gene; *DTA*, diphtheria toxin A gene; *DTR*, diphtheria toxin receptor gene; *LPo*, optimized flippase-recombinase gene; mTmG, loxP-tdTomato-STOP-loxP-GFP; FKBP–Casp8–*FK506*-binding-protein caspase 8 gene.

improved *in vivo* models for investigation of senescent TAMs have been suggested in recent years. All this would facilitate detailed characterization of this subpopulation of myeloid cells in tumors and expand our understanding of the role of senescent TAMs in oncogenesis in the nearest future. We hope that the progress in methodology of investigation of senescent TAMs discussed in this review will help the readers to select appropriate strategy in investigation of various aspects of tumor growth. Senescent TAMs, as a separate population of cells, deserves special attention of the researchers; the recently introduced new class of therapeutic preparations, senolytics, which limit negative effects of the senescent cells by changing the fraction of senescent cells in the tumor microenvironment, could increase significantly efficiency of various anticancer therapies.

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