CHAPTER

11

Membrane Type-1 Matrix Metalloproteinase-Regulated Autophagy: A Role in Brain Cancer Chemoresistance

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OUTLINE

Abstract

Autophagy is recognized as being involved in several stages of the growth and metastasis of central nervous system tumors, and can both impede and promote tumor development. In order to adapt to the stresses of low oxygen and low nutrients cancer cells express autophagic activity which allows them to maintain a sufficient nutrient supply, and which plays important roles in the immune response as well as in the control of reactive oxygen species. Consequently, dysregulated autophagy has recently been described as a new hallmark of brain cancer cells that explains, in part, their resistance to current treatments. Among the chemoresistance

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mechanisms and key players recently characterized in brain cancer cells, membrane type-1 matrix metalloproteinase (MT1-MMP) has recently been shown to relay inflammatory and autophagy signaling and may therefore represent a promising target. More importantly, modulation of the intracellular functions of MT1-MMPs by MTCBP-1, a cytoplasmic MT1-MMP binding partner, is believed to regulate the autophagy index from low-to-high grade glioblastomas. In this chapter, we will discuss the global roles and functions of MMPs in autophagy and more specifically, the importance of MT1-MMP-mediated signaling in autophagy.

Abbreviations

Å	Ångstrom
AG490	Tyrphostin (Inhibitor of JAK2)
AKT	Protein kinase B
AMPK	Adenosine monophosphate kinase
ARP101	Inhibitor of MMP-2
ATG	Autophagy-related gene
ATP	Adenosine triphosphate
Bcl-2	B-cell lymphoma 2
BNIP3	BCL2/adenovirus E1B 19 kDa protein-interacting protein 3
CNS	Central nervous system
Con-A	Concanavalin-A
COX-2	Cyclooxygenase 2
Cyto-D	Cytochalasin-D
DAMP	Damage-associated molecular pattern
DNA	Deoxyribonucleic acid
DRAM	Damage-regulated modulator of autophagy
ECM	Extracellular matrix
EGCG	Epigallocatechin 3-gallate
EGFR	Epidermal growth factor receptor
ER	Endoplasmic reticulum
FAK	Focal adhesion kinase
FRET	Fluorescence resonance energy transfer
gC1qR	Receptor for the globular heads of C1q
HIF-1	Hypoxia-inducible factor-1
JAK2	Janus kinase 2
LC3	Microtubule-associated protein 1A/1B-light chain 3
MMP	Matrix metalloproteinase
MT1-MMP	Membrane type-1 MMP
MTCBP-1	MT1-MMP cytoplasmic binding protein-1
mTOR	mammalian target of rapamycin
NF-κB	Nuclear factor-kappa B
p130Cas	Breast cancer anti-estrogen resistance protein 1
p53	Tumor protein p53
p62	Nucleoporin p62 complex
p-70S6K	p-70S6 ribosomal kinase
PI3K	phosphoinositide 3-kinase
PTEN	Phosphatase and Tensin homolog
RhoA	Rho GTPase
ROS	Reactive oxygen species
SPR	Surface plasmon resonance
STAT3	Signal transducer and activator of transcription 3
TIMP	Tissue inhibitor of metalloproteinase
TLR	Toll-like receptor
Tyr573	Tyrosine in position 573

INTRODUCTION

Barriers to Brain Cancer Growth

In order for tumors to grow, multiply, and metastasize they must respond to a battery of challenges which serve to eliminate the vast majority of microtumors before they can become established (Vanharanta and Massagué, 2013). In order for a metastatic cell to invade a foreign site, it must exit from the blood or lymphatic vessels, enter the new site, and form extracellular matrix (ECM) links there (Su et al., 2015). The growing tumor then requires angiogenesis to supply it with sufficient nutrients and oxygen, and it also must be able to continue to replicate without limits, avoiding cellular latency. For this, cancer cells require self-sufficiency with respect to growth signals and must be able to ignore the physiological signals which generally halt proliferation; they must also prevent the apoptosis or necrosis that is often upregulated by these signals. A solid tumor must be able to withstand not only living within the inflammatory conditions that are generally produced at its new site, but also to evade the immune attack that is mounted against it. In addition, the cell must reprogram its metabolism to enable it to survive under these hostile conditions and it must be able to withstand the genomic instability that is produced by the response to its untrammeled growth. Finally, the tumor must be able to shed metastatic masses which are able to leave this site. Autophagy plays a role in a number of these barriers, either as part of the barrier to tumor growth or in the mechanisms of the tumor for overcoming barriers; we will discuss a few of them here.

The generation of nutrients and energy in response to starvation or other metabolic stress conditions is required for rapidly growing tumor cells, which utilize autophagic processes to obtain these nutrients, thus promoting cell survival. In response to numerous stress conditions, autophagy has been shown to protect dormant cells, enabling them to resume growth under more favorable conditions (Mathew and White, 2011). These conditions activate hypoxia-inducible factor-1 (HIF-1) and 5′-AMP-activated kinase (AMPK) which stimulate autophagy, thus supplying nutrients for the cell, maintaining homeostatic conditions, and allowing the cell to survive (Ávalos et al., 2014). The utility of this mechanism for tumor cells, which are chronically hypoxic and lacking sufficient blood supply, is obvious.

The autophagy pathways play a role in control of the immune response (Arroyo et al., 2014). Stimulation of microglial toll-like receptors (TLRs) in the central nervous system (CNS) by a stimulatory antigen leads to autophagic activation of these cells and, eventually, to autophagic cell death (Arroyo et al., 2014). Mammalian target of rapamycin (mTOR), a central player in autophagic control, has also been shown to be involved in the pro-inflammatory activation of microglia (Lu et al., 2006). While the number and identity of the signaling pathways linking inflammation and tumorigenesis is not clear, the number of inflammatory stimuli is far greater than the number of transcriptional factors that they activate, suggesting that understanding these pathways may provide useful targets for braking tumor growth (Sen, 2011).

The accumulation of reactive oxygen species (ROS) poses a considerable threat to cancer cells as they derange cellular signaling and can directly oxidize lipids and proteins or cause breaks in DNA; the ROS can arise from internal generation due to enhanced metabolism or are due to necrosis in the environment of the cell (Liou and Storz, 2010; Mah and Ryan,

2012). One of the major roles of autophagy in preventing tumor growth is the diminution of ROS levels, thus preventing the oxidations and breaks in DNA which would threaten the cell (Kaza et al., 2012). Conversely, the deleterious effects of ROS are enhanced when autophagy is diminished (by use of inhibitors or genetic removal of essential autophagic genes), allowing the accumulation of damaged mitochondria which would normally be destroyed via the autophagosome and thus increasing the ROS load (Giuliani and Dass, 2014).

A number of molecules serve as damage-associated molecular patterns (DAMPs) which are either released into the extracellular space or concentrated in the outer leaflet of the plasma membrane; these include ATP and uric acid (Gallo and Gallucci, 2013). Recognition of DAMPs by the immune system occurs via a large family of receptors. The production and trafficking of these DAMPs occurs via the autophagic machinery. It has also been suggested that DAMPs are not simply products of autophagic processing but are also powerful stimulants of it as well (Hou et al., 2013).

One significant barrier to understanding the role of autophagy in the control of tumor growth is interplay between the control of apoptosis, necrosis, and autophagy (Su et al., 2015). Cancer cells often evade these three methods of destruction by mutation of the factors modulating them, and there is considerable overlap in the identity of the proteins controlling these processes. Though the specific mechanisms controlling autophagy are complex and remain poorly understood, it is clear that the mTOR complex inhibits autophagy whereas the phosphatase PTEN promotes it; in many tumors, PTEN is one of the initial genes mutated, leading to constitutive inhibition of autophagy along with enhanced translation and cell growth (Bhutia et al., 2013). Similar results are seen for several other proteins which are crucial for autophagy control, such as AKT and DRAM. The resultant lack of autophagy prevents autophagic death from removing the proliferating cells in which the mutated proteins have arisen. However, modulation of autophagy is now well-recognized as increasing the lethality of chemotherapy and radiotherapy against tumors (Kaza et al., 2012). In brain tumors, lower expression of beclin-1 has been shown to correlate with decreased apoptosis and increased cell proliferation (Kaza et al., 2012). It is clear that autophagy can act both to enhance and to combat tumor metastasis, depending on both the type of tumor and the specific stage of metastasis (Su et al., 2015).

Resistance to Current Treatments for Brain Cancer

Brain cancers, most prominently glioblastoma multiforme, are amongst the most lethal forms of cancer (Persano et al., 2013). Despite decades of research into combatting these diseases, the mortality rate has changed little, largely due to the evolution of a chemoresistance phenotype within the tumors. A number of different mechanisms have been shown to underlie cancer chemoresistance, encompassing different aspects of cell physiology (Housman et al., 2014). Some of these mechanisms involve inactivation of the drug by chemical modification (or blocking of modifications required to activate the drug), removal of the drug from the cancer cells by active efflux across the cell membrane, or alteration of the drug target itself. Other mechanisms involve repair of the damage induced within the DNA of the cell, usually by alkylating agents or platinum, or inhibition of cell death through modulation of apoptosis or autophagy. The extremely unfavorable prognosis for patients

suffering from glioblastomas has been strongly correlated to inefficient targeting of their intrinsic apoptosis resistance phenotype (Pratt et al., 2012).

The diffuse infiltrative phenotype of gliomas within the normal brain tissue of patients (Stewart, 2002) combined with the recently reported presence of glioma-initiating cells are believed to be conditions that favor the initiation and recurrence of glioblastoma (Zhuang et al., 2011). Autophagy was shown to play an essential role in the regulation of the glioma-initiating cells tumorigenic potential (Zhuang et al., 2011). Since the groups currently defining staging for neoplasms assess and incorporate measures for the presence of apoptosis, autophagy, and necrosis (Demaria et al., 2010), this suggests that autophagy could be considered as a promising therapeutic target for specifically defined subsets of glioblastomas.

ECM DEGRADATION AND MATRIX METALLOPROTEINASES: A LINK TO THE CHEMORESISTANCE PHENOTYPE

One of the most important biological processes governing the destiny of the cell for growth or death is its interaction with the ECM. This chapter describes the evidence for HA/CD44v3-mediated activation of the cytoskeleton (e.g., ankyrin and GTPases) and matrix metalloproteinase (MMP) signaling during tumor progression. Interestingly, the protein digestion products produced by MMPs can also stimulate autophagy by inducing ECM detachment and rearrangement (Lock and Debnath, 2008). Although these mechanisms are not fully understood, recent findings showed that loss of β1-integrin, epidermal growth factor receptor (EGFR), and focal adhesion kinase (FAK) promotes both autophagy and ECM detachment (Reginato et al., 2003; Gan et al., 2006; Fung et al., 2008). Decorin, the most studied proteoglycan, was further shown to exhibit important functions in both ECM reorganization and induction of autophagy, including EGFR downregulation (Wei et al., 2013). Other members of the proteoglycan family such as endorepellin, syndecans, glypicans, collagens IV and VI, and endostatin are also involved in ECM remodeling, but their roles in autophagy are still under investigation (Iozzo and Sanderson, 2011; Neill et al., 2014). Moreover, in normal cells, ECM detachment leads to a specific form of apoptotic cell death called anoikis (Gilmore, 2005). On the other hand, brain cancer cells have the ability to resist anoikis by promoting both autophagy and metastasis (Kenific et al., 2010; Zhang et al., 2011). Since the mechanisms that link autophagy (and resistance to anoikis) to the resistance phenotype are not fully understood, it is possible that part of the answer is the involvement of MMPs, which are known to cleave important ECM molecules, like proteoglycans, integrins, and adhesion proteins (Taraboletti et al., 2002; Conant et al., 2010; Kesanakurti et al., 2012; Manon-Jensen et al., 2013).

Matrix Metalloproteinases

MMPs are the best-known group of proteolytic enzymes that affect the ECM and they are also the main group of regulating proteases there (Theocharis et al., 2014). The MMPs are proteins, produced by 23 human genes, which are related on the basis of structural similarity and function. They all (i) bind a zinc ion, (ii) have an initial, latent conformation but are converted to an active conformation following protease activation, (iii) are inhibited by

one or more of the tissue inhibitors of metalloproteinases (TIMPs), (iv) can digest at least one of the ECM proteins, and (v) bear strongly conserved amino acid sequences within their catalytic domains (Andreini et al., 2004). The MMPs are best known for digesting a wide variety of the structural proteins which comprise the ECM, but are also able to digest many other proteins, extending the physiological utility of these proteins. Remodeling of the ECM is one of the principal steps in cancer metastasis and it relies on the activities of proteolytic enzymes for the digestion of the structural proteins and proteoglycans located there. Different combinations of MMPs are expressed in all cells.

Most of the MMPs are soluble proteins, with a highly conserved structure bearing four domains (Bode et al., 1999). The majority bear an N-terminal signal sequence to enable secretion across the cell membrane, followed by a pro-peptide domain that may or may not end in a furin cleavage site. The pro-peptide domain forms a fold which effectively covers the next domain, a catalytic protease domain with strong sequence conservation, containing the zinc-binding site. Following the catalytic domain is a hinge region which is usually followed by the last common domain, containing four hemopexin-like repeats, that appears to function in substrate binding to the MMP. This latent, inactive conformation is generally maintained by a cysteine switch sequence in the pro-peptide region which binds to the zinc ion. After the enzyme has been released as a zymogen, it is activated when cleaved by other proteases, such as other MMP molecules. The proteolytic activity of MMPs on nonmatrix substrates has been shown to cause activation or inactivation of a broad host of signaling molecules, such as chemokines, cytokines, and growth factors (Nissinen and Kähäri, 2014). Table 11.1 lists the nature of the various human MMPs and describes whether their levels of expression have been shown to be correlated with autophagy, along with a description of the cell lines or tissues in which the work was performed. It should be noted that high levels of MMPs have been described in tumors of the CNS (Forsyth et al., 1999).

Despite the involvement of many MMPs in autophagy, we have chosen to concentrate our efforts on the membrane-bound members of this family (MT-MMPs) due to their roles in the modulation of cell signaling; four of these proteins (MMP-14, MMP-15, MMP-16, and MMP-24) contain transmembrane domains and we have focused on MMP-14 (MT1-MMP), which is the best-characterized of this class.

MEMBRANE TYPE-1 MATRIX METALLOPROTEINASE

The membrane type-1 MMP (MT1-MMP) is expressed in most tissues and has wide substrate specificity, encompassing many of the proteins found in the ECM. MT1-MMP knockout mice exhibit dysfunctional connective tissue metabolism and abnormal development of teeth and lungs. The complex significance of MT1-MMP in cancer can be seen in that glioma-associated microglia have been shown to induce and exploit MT1-MMP expression for tumor expansion, whereas MT1-MMP overexpression in glioma cells was lethal (Markovic et al., 2009). While this significance may be due to its well-known role in the activation of pro-MMP-2 and its intrinsic proteolytic activity ECM molecules, many other new functions have been assigned to MT1-MMP. Recent roles of MT1-MMP have been shown for bioactive lysophospholipid signaling (Annabi et al., 2009a), nuclear factor-kappa B (NF-κB)-mediated cyclooxygenase (COX)-2 regulation (Han et al., 2001; Annabi

TABLE 11.1 Roles for MMPs in the Regulation of Autophagy

Metalloproteinases (Enzyme Type)	Tissues or Cell Types	Autophagy to MMP Correlation	Autophagy Biomarkers Assessed	References
MMP-1 (Collagenase 1)	Breast cancer cells (MDA-MB-231)	Positive	↑LC3	Augustin et al. (2009)
	Human primary RCC, CA-TC, and GR-TC	Positive	↑LC3	Tringali et al. (2012)
	Human dermal fibroblasts	Positive	↑LC3	Tashiro et al. (2014)
MMP-8 (Collagenase 2)	Periodontal Ligament Cells	Positive	↑LC3	Song et al. (2012)
MMP-13 (Collagenase 3)	Nucleus pulposus (rat spinal column)	Negative	↑LC3	Jiang et al. (2014)
			↑p-mTOR	
			↑p-70S6K	
	Mouse knee joints	Negative	↓LC3	Hui et al. (2014)
	Human osteoarthritic and nonosteoarthritis cartilage	Negative	↓Beclin-1	Song et al. (2014)
			↓ATG7	
			↓LC3	
	Articular chondrocytes from *Col2a1-CreER^{T2}; Vhl$^{fl/fl}$* mice	Negative	↓Beclin-1	Weng et al. (2014)
			↓LC3	
	Mouse cardiomyocytes	Positive	↑P62	Qipshidze et al. (2012)
			↑LC3A/B	
MMP-2 (Gelatinase A)	Mouse cardiomyocytes	Positive	↑P62	Qipshidze et al. (2012)
			↑LC3A/B	
	LX-2 cells, an immortalized human HSCs line	Positive	↑P62	Lee et al. (2014)
			↑LC3II	
	Human osteoarthritic and nonosteoarthritic cartilage	Negative	↓Beclin-1	Song et al. (2014)
			↓ATG7	
			↓LC3	
	Human tongue carcinoma cell lines	Negative	↓ATG4	Weng et al. (2014)
			↓ATG5	
			↓LC3II	
	Mixed glial cultures from day-old mice	Negative	↓Beclin	Caldeira et al. (2014)
			↓LC3II	
MMP-9 (Gelatinase B)	Mouse cardiomyocytes	Positive	↑P62 ↑LC3A/B	Qipshidze et al. (2012)

(*Continued*)

TABLE 11.1 (Continued)

Metalloproteinases (Enzyme Type)	Tissues or Cell Types	Autophagy to MMP Correlation	Autophagy Biomarkers Assessed	References
	Rat brain endothelial cells (primary ECs)	Positive	↑LC3II	Engelhardt et al. (2015)
	Human hepatocellular carcinoma samples from patients	Positive	↑LC3II	Li et al. (2015)
	HTR8/SVneo, HchEpClb (extravillous trophoblast cell lines)	Positive	↑LC3II	Yamanaka-Tatematsu et al. (2013)
	HepG2 and BEL7402 (Hepatocellular carcinoma cell lines)	Positive	↑LC3II	Li et al. (2013)
	$P8^{-/-}$ and $P8^{+/+}$ mice cardiomyocytes	Positive	↑LC3 ↑Conjugation of ATG5-ATG12 ↓p62	Georgescu et al. (2011)
	MCF-10A, MCF-7, and 240Lp16sMY cells	Positive	↑LC3	Girard et al. (2015)
MMP-3 (Stromelysin 1)	Embryonic stem cell-derived odontoblast-like cells	Positive	↑ATG5 ↑LC3 ↑ATG12	Ozeki et al. (2015)
	Human osteoarthritis and nonosteoarthritis cartilage	Negative	↓Beclin-1 ↓ATG7 ↓LC3	Song et al. (2014)
MMP-7 (Matrilysin 1)	Human primary RCC, CA-TC, and GR-TC cells	Positive	↑LC3	Tringali et al. (2012)
MMP-14 (MT1-MMP)	Glioblastoma cells (U87)	Positive	↑LC3 ↑BNIP3 ↑ATG3 ↑ATG12 ↑ATG16L1 ↑ATG16L2	Pratt et al. (2012)
	Glioblastoma cells (U87)	Positive	↑LC3	Pratt and Annabi (2014)
	Glioblastoma cells (U87)	Positive	↑LC3	Pratt et al. (2016)
MMP-19 (Macrophage elastase)	Primary mouse lung fibroblasts (*MMAP19*$^{+/+}$ and *MMP19*$^{-/-}$)	Positive	↑ATG4c	Jara et al. (2015)

Studies which have found correlation between a specific MMP and autophagy (e.g., using expression of essential autophagic proteins) are listed along with the cell types (or tissues) used and the effects observed.

et al., 2009b; Sina et al., 2010), radioresistance in both glioma (Wild-Bode et al., 2001; Wick et al., 2002) and endothelial cells (Annabi et al., 2003a), and as a cell death sensor/effector (Belkaid et al., 2007; Currie et al., 2007; Proulx-Bonneau et al., 2011a). While a role for MMPs in autophagic cell death has been suggested (Augustin et al., 2009), the exact mechanisms involved and their biological significance remain largely unexplained.

MT1-MMP is among the biomarkers shown to trigger both apoptotic and autophagic signaling events (Annabi et al., 2003c; Markovic et al., 2009; Pratt et al., 2012). Given the recent links between endoplasmic reticulum (ER) stress, apoptosis, and autophagy (Schleicher et al., 2010; Benbrook and Long, 2012), the intracellular signaling roles of the MT1-MMPs become even more relevant since ER stress was also found to be induced in glioblastoma cells overexpressing MT1-MMP (Proulx-Bonneau et al., 2011a). Finally, exploiting the altered metabolism that characterizes brain tumor cells (Wolf et al., 2010; Galeffi and Turner, 2012), MT1-MMP was found to transcriptionally downregulate the expression of a microsomal glucose-6-phosphate transporter, whose elevated expression in glioblastoma controls cell survival (Belkaid et al., 2006), and whose downregulation in cells overexpressing MT1-MMP triggered cell death (Belkaid et al., 2007). In fact, glucose-6-phosphate transporter has recently been suggested to act as a key regulator functioning at the autophagy initiation step (Ahn et al., 2015). MT1-MMP activity is physiologically controlled by a number of stressors, including hypoxia and inflammation. When using *in vitro* experimental settings, a more practical approach to mimic such stressors is to use pharmacological means such as exposure to Concanavalin-A (Con-A) or to Cytochalasin-D (Cyto-D). Given that Con-A and Cyto-D are able to induce MT1-MMP expression (Sina et al., 2010), it should be possible to envision that therapeutic targeting of the MT1-MMP activity of the body would complement cancer treatment. Since Con-A is known to induce autophagic cell death in many types of cancer, lectin-induced autophagy is therefore one such potential therapeutic avenue (Lei and Chang, 2009).

The intracellular events involved in MT1-MMP signal transduction are currently under heavy investigation. The intracellular domain-mediated signaling of MT1-MMPs triggers events that lead to phosphorylation of numerous signaling intermediates including signal transducer and activator of transcription 3 (STAT3) (Zgheib et al., 2013), extracellular signal-regulated kinase (Gingras et al., 2001), and NF-κB (Sina et al., 2010), as well as inducing the expression of RhoA (Annabi et al., 2005). It is not known whether these activities require intracellular binding partners to interact with the 20 amino acid intracellular domain of MT1-MMP. However, numerous MT1-MMP cytoplasmic domain-binding proteins have been identified, such as the μ2 subunit of adapter protein 2, gC1qR, p130Cas, MTCBP-1, and the phosphorylated form of caveolin-1 (Annabi et al., 2002; Lei and Chang, 2007; Shingu et al., 2009; Brahimi-Horn et al., 2011; Kaza et al., 2012). The cytoplasmic domain of MT1-MMP was further demonstrated to ultimately promote the invasive activity of MT1-MMP by preventing its internalization (Annabi et al., 2002). It remains unknown whether any of the above-mentioned MT1-MMP intracellular binding intermediates are involved in autophagy regulation or in autophagy biomarker induction. Given the high level of sequence identity between the transmembrane and cytoplasmic regions of the four membrane-type MMPs (see Fig. 11.1), it is tempting to speculate that the other three proteins demonstrate autophagy-related activities similar to MT1-MMP. However, we do not know of any investigations which have been carried out with these proteins.

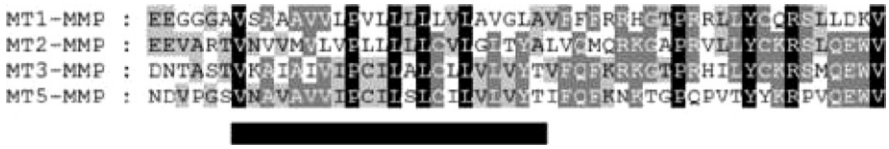

FIGURE 11.1 Alignment of the carboxyl regions of the MMPs containing transmembrane domains. The terminal, carboxyl sequences of the four human MT-MMP proteins are shown after alignment. A black background indicates where an individual amino acid is conserved in all four of the proteins, a dark gray background indicates where an amino acid is found in three of the four, and light gray indicates sequence identity in two of the four proteins. The horizontal black bar shown beneath the sequences denotes the location of the transmembrane domain.

DISCUSSION

Targeting Autophagy to Fight Cancer

Current conventional cancer therapies fail to mediate their effects in a target-specific fashion (Quant et al., 2010; Sampson et al., 2011). One reason is that the extremely unfavorable prognosis for patients suffering from glioblastomas strongly correlated with inefficient targeting of the intrinsic apoptosis resistance phenotype. Aside from apoptosis-based therapies, induction of autophagic cell death is an alternate and emerging concept for triggerring glioma cell death and exploiting caspase-independent programmed cell death pathways for the development of novel glioma therapies (Kögel et al., 2010). Induction of autophagic cell death may therefore help stop tumor development and optimize cancer treatment modalities (Ceteci et al., 2011; Guo et al., 2011; Chen et al., 2012). Interestingly, the clinically approved antibiotic minocycline, a highly lipid-soluble antibacterial known for its ability to cross the blood–brain barrier, is a promising new candidate for adjuvant therapy against malignant gliomas since it reduces MT1-MMP expression (Markovic et al., 2009). More importantly, minocycline effectively inhibited tumor growth and induced autophagy in a xenograft tumor model of C6 glioma cells (Liu et al., 2011a) though it is unknown whether MT1-MMP is involved in this.

While the specific roles of MMP in autophagy still remain to be unraveled, chemical modulators of autophagy, such as the selective MMP-2 inhibitor ARP101 (Jo et al., 2011), seem to offer some potential for treatment of these diseases although the precise molecular mechanism of action remains unknown. Interestingly, it was recently reported that the molecular mechanism of action of Brefeldin-A, another well-known autophagy regulator, operates through sequestration of MT1-MMP and induction of ER stress (Proulx-Bonneau et al., 2011a). This new role of a membrane-bound MMP in transducing Brefeldin-induced ER stress signaling is supported by emerging data which indicates that ER stress is also a potent inducer of macroautophagy (Matus et al., 2008; Yin et al., 2012). It is currently unclear whether this process enhances cell survival or commits cells to nonapoptotic death (Høyer-Hansen and Jäättelä, 2007).

In cancer cells, induction of autophagy serves as an adaptive response that can lead to chemoresistance mechanisms and increased cell survival (Reuter et al., 2010), effects which are also associated with high cellular MT1-MMP levels (Trog et al., 2006). Thus, the

inhibition of autophagy combined with induction of metabolic stress or chemotherapeutic agents could enhance effective anticancer therapy by inhibiting stress adaptation and increasing cell killing. Pharmacological approaches have demonstrated that diet-derived epigallocatechin 3-gallate (EGCG), a polyphenol shown to trigger autophagy (Li et al., 2011) and to sensitize cells to radiation (McLaughlin et al., 2006), as well as mTOR inhibitors such as rapamycin, can be used to increase the radiosensitivity of glioblastoma cells by the induction of autophagy (Zhuang et al., 2009). In support of a possible role for MT1-MMP in intracellular transduction events rapamycin was recently shown to upregulate MT1-MMP expression in PTEN(+/+) cells via PI3K activity (Kim et al., 2010). Tumor suppressors like Beclin-1, PTEN, and p53 are also crucial players in the induction and regulation of autophagy (Liu et al., 2011b).

Controlling MT1-MMP activity might also be possible by targeting the proteins which interact with this proteinase, such as BCL2/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3). BNIP3 is an atypical representative of the Bcl-2 protein family and a regulator of nonapoptotic programmed cell death (Swoboda and Strzadała, 2009), which was demonstrated to interact with microtubule-associated protein 1A/1B-light chain 3 (LC3) and to promote autophagy of both mitochondria and ER (Hanna et al., 2012) as well as to participate in the activation of autophagy by mediating 6-thioguanine and 5-fluorouracil-induced autophagy (Zeng and Kinsella, 2010). BNIP3 expression correlates with the induction of acidic vesicular organelles both by ConA and directly upon MT1-MMP overexpression, suggesting that BNIP3 expression may serve as an autophagy biomarker consequent to MT1-MMP-mediated signaling in glioblastoma cells. Accordingly, BNIP3 expression levels are correlated with a signaling cascade in which MT1-MMP is a major contributor and which requires phosphorylation of STAT3. Interestingly, increased JAK2/STAT3 signaling was also correlated with increased apoptosis through upregulation of BNIP3 gene expression (Bulcao et al., 2010). Further evidence that MT1-MMP affects BNIP3 expression was seen when upregulation of BNIP3 and of autophagy-related gene members ATG3, ATG12, and ATG16-L1 expression in ConA-treated U87 cells were reversed when MT1-MMP gene expression was silenced (Pratt et al., 2012). Finally, the pharmacological JAK inhibitors AG490 and Tofacitinib confirmed the requirement for JAK2 in the induction of BNIP3; whether any recruitment and/or interaction between JAK2 and MT1-MMP are required remains unknown. There is a mandatory requirement for the cytoplasmic domain of MT1-MMP in the induction of BNIP3, although whether this structural requirement involves recruitment and/or interaction with specific intracellular intermediates is currently unknown.

Given the recent report that BNIP3 acts as transcriptional repressor of apoptosis-inducing factor expression and prevents cell death in human malignant gliomas (Burton et al., 2009), this links the possible contribution of MT1-MMP to the radioresistance and chemotherapeutic resistance index of brain tumors. BNIP3 is expressed at high levels in solid tumors, including glioblastoma, where its nuclear location is believed to confer a survival advantage to glioma cells (Burton et al., 2006). BNIP3 upregulation under hypoxic conditions by the transcription factor HIF-1 remains open for debate (Namas et al., 2011; Zhao et al., 2012), but was demonstrated to locate within hypoxic regions of tumors (Sowter et al., 2001). Given the demonstrated role of MT1-MMP in hypoxia-regulated events (Proulx-Bonneau et al., 2011b), it is tempting to assume similar events taking place in the MT1-MMP-mediated regulation of BNIP3 in autophagy.

The development of therapeutic strategies targeting the transducing events mediated by the intracellular domain of the MT1-MMPs can also be envisioned. Structure-function studies have already confirmed that MT1-MMP induces the expression of biomarkers such as cyclooxygenase-2 in inflammation (Annabi et al., 2009b; Proulx-Bonneau et al., 2011a), BNIP3 in autophagy (Pratt et al., 2012), endothelial tubulogenesis (Pilorget et al., 2005) and apoptosis (Belkaid et al., 2007). ConA was also confirmed to trigger autophagy (Lei and Chang, 2007) and to, in part, require MT1-MMP-mediated signaling; inhibition of the intracellular domain Tyr573 phosphorylation of MT1-MMP by either genistein (Li et al., 1997; Yu et al., 1997) or through site-directed mutagenesis (Zgheib et al., 2013), inhibited ConA-induced autophagy. The ConA-induced signaling cascades, in which MT1-MMP serves as an intermediate, were also recently found to be triggered and highlighted a role for transcription factors including NF-κB (Sina et al., 2010), STAT3 (Akla et al., 2012), and HIF-lα (Proulx-Bonneau et al., 2011b). Pharmacological strategies targeting MT1-MMP functions have used tetra- and hexavalent mannosides, which inhibit the pro-apoptotic effects of ConA (Fortier et al., 2008), and EGCG which inhibits the expression of colony-stimulating factors-2 and -3 (Zgheib et al., 2013). Whether these agents also modulate MT1-MMP-mediated autophagy remains to be seen. Finally, gene silencing of p130cas, another MT1-MMP interacting partner in endothelial cells (Gingras et al., 2008) whose expression is associated with poor clinical outcome in human ovarian carcinoma (Nick et al., 2011), decreased tumor growth through stimulation of combined apoptotic and autophagic cell death (Nick et al., 2011).

MTCBP-1

One protein with an important relationship to MT1-MMP is MTCBP-1; there is increased MT1-MMP expression in high grade tumors but increased MTCBP-1 expression in low grade tumors. In addition, we have shown that MTCBP-1 binds directly to the intracellular domain of MT1-MMP and presumably mediates some of the interactions between MT1-MMP and the signaling mechanisms known to be affected by MT1-MMP, thereby regulating the intracellular function of MT1-MMP-mediated autophagy (Pratt et al., 2016). MTCBP-1 abrogates the MT1-MMP-mediated signaling that triggers autophagy, suggesting that high grade brain tumors may possibly exhibit unregulated MT1-MMP-mediated autophagy processes that enable these cancers to escape the cell death-inducing therapeutic modalities that trigger, in part, cell autophagy. Since cellular stresses such as hypoxia induce both autophagy (Brahimi-Horn et al., 2011) and MT1-MMP (Annabi et al., 2003b; Proulx-Bonneau et al., 2011b), these adaptive mechanisms may help established tumors to survive (Eskelinen, 2011). Beyond the evidence that MT1-MMP shows both pro-apoptotic and pro-autophagic transducing properties, we have shown that MTCBP-1, in addition to inhibiting MT1-MMP-mediated cell invasion (Uekita et al., 2004), abrogated the ability of MT1-MMP to trigger autophagy. Given that MTCBP-1 expression is low in highly invasive tumors, this observation strengthens the concept that high grade brain tumors possess cell death-escaping properties, possibly through dysregulated autophagy. Supporting this, an oligonucleotide microarray of metastasis-related genes in genistein-treated HCC1395 breast cancer cells demonstrated upregulated MTCBP-1 expression (Lee et al., 2007).

The resistance to apoptotic cell death, a hallmark of most cancers, has driven the search for novel targets in cancer therapy. The autophagy pathway is one such target currently being explored for multiple cancers including gliomas, and is a promising avenue for further therapeutic development (Kaza et al., 2012). Better understanding of autophagy regulation and of autophagy-inducing mechanisms is therefore an emerging area of interest in brain cancer research. Given that progression of astrocytic tumors into more aggressive and chemoresistant phenotypes is partly related to their decreased autophagic capacity (Huang et al., 2010), appropriate modulation of autophagy may therefore sensitize tumor cells to anticancer therapy (Shingu et al., 2009).

In conclusion, the signaling balance involved in the modulation of the autophagy index seems crucial in dictating survival or death for cells during metabolic adaptation and tumor progression. The MT1-MMP-to-MTCBP-1 expression ratio may be one of these dichotomous processes. Although we cannot exclude the contribution of potential third partners, FRET analysis data indicates the molecular proximity of MTCBP-1 and MT1-MMP intracellular domain at distances ranging from 10 to 100 Å while surface plasmon resonance analysis data indicates specific interaction between MTCBP-1 and the intracellular MT1-MMP domain. We believe that identification and functional characterization of intracellular MT1-MMP binding partners, such as MTCBP-1, may enable the development of future therapeutic strategies aimed at exploiting intracellular MT1-MMP transducing functions which contribute to the invasive and chemoresistant phenotype of glioblastoma.

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