THE ROLE OF MONOGLYCERIDE LIPASE IN APOPTOSIS AND INFLAMMATION

By

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DISSERTATION ABSTRACT

The Role of Monoglyceride Lipase in Apoptosis and Inflammation

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Monoglyceride lipase (MGL) is lipase that hydrolyzes a variety of monoglycerides, by which it plays an important role in lipid metabolism. Previous studies in our laboratory showed that MGL expression was either reduced or absent in the majority of the cancer tissues that we screened as compared with their normal matching tissues, implying that MGL is a potential tumor suppressor.

To further elucidate the function of MGL in tumorigenesis, we generated MGL-knockout mouse to assess tumor formation in the absence of MGL expression. We found that MGL knockout led to tumor formation in a number of different tissues in mice and lung adenocarcinoma was the predominant phenotype. Our screening of human lung tissues also showed that MGL expression was either reduced or absent in cancer tissues as compared with adjacent normal tissues. The findings altogether strongly suggest that MGL plays a tumor suppressive role in lung cancer. Mechanistically, we determined that MGL deficiency led to enhanced EGFR signaling and up regulation of COX-2 expression in lung cancer cells, both of which were known to promote tumor formation and progression. Moreover, our recent study identified there was direct interaction between MGL and IκB and this interaction was critical for the inhibition of NF-κB activity. These

findings are highly consistent with our observation of inflammatory responses in the MGL-deficient lung tissues.

Previously we found that MGL over-expression induced cell death in multiple cancer cell lines. Recently we determined that MGL was a negative regulator of XIAP. Furthermore, we showed that MGL directly interacted with and destabilized XIAP protein. Our data suggest that this effect of MGL is responsible for the suppression of the anti-apoptotic function of XIAP as well as the induction of apoptosis.

Overall, our previous and recent findings all support the notion that MGL is a tumor-suppressor. In addition, our new studies have demonstrated the important roles of MGL in the modulation of tissue inflammation and apoptosis. These may prove to be signifiant discoveries that will inspire future studies to elucidate the function of MGL in the context of other diseases other than cancer.

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GENERAL INTRODUCTION

Monoglyceride lipase

In 1976, a new potential lipase (now known as Monoglyceride lipase, MGL, MAGL, or MGLL) in rodent was first discovered and reported by studies of Tornqvist and Belfrage (1976). From the rat adipose tissue extract, they identified a new protein that processed properties of monoacylglycerol hydrolyzing activity (Tornqvist and Belfrage, 1976). It was estimated this new enzyme protein to have a molecular mass of ~32,900 Dalton (Tornqvist and Belfrage, 1976). Under the assay conditions, the enzyme was found to hydrolyze 1(3)- and 2-monooleoylglycerol at equal rates but did not catalyze the hydrolysis of other lipids such as emulsified trioleoylglycerol, micellar or emulsified dioleoylglycerol, emulsified cholesterol oleate or micellar lysophosphatidylcholine. It was therefore considered as an enzyme to have specific monoacylglycerol hydrolase activity (Tornqvist and Belfrage, 1976). Later in 1997, the mouse monoglyceride lipase (MGL) cDNA was first identified and cloned by the Holm's group from a mouse adipocyte cDNA library (Karlsson et al., 1997). The reported mouse monoglyceride lipase cDNA contained 912 nucleotides and predicted as a protein with 303 amino acids with a molecular mass of 33,218 Dalton. At the time, the cDNA and protein of human monoglyceride lipase had not yet been identified and reported, thus, the authors did not find the mouse monoglyceride lipase cDNA and protein to have extensive homology to any known mammalian cDNAs and proteins (Karlsson et al., 1997). However, the mouse monoglyceride lipase was found to be distantly related to number of microbial proteins, including two bacterial lysophospholipases and a family of haloperoxidases (Karlsson et

al., 1997). The predicted amino acid sequence of mouse monoglyceride lipase harbored a catalytic triad of serine lipase which contained a serine residue (Ser-122) within a GXSXG lipase motif as well as residues of Asp-239 and His-269 (Karlsson et al., 1997). Mouse monoglyceride lipase mRNA was found to be expressed in all mouse organs and when exogenously expressed in COS cells, it exhibited lipase activity for hydrolyzing mono-[3H]olein (MO) and esterase activity for hydrolyzing p-nitrophenyl butyrate (PNPB) (Karlsson et al., 1997). Site-directed mutations at the key residues of the catalytic triad, for example, S122A, D239N and H269A, significantly abolished the activity of mouse MGL as lipase and esterase (Karlsson et al., 1997).

Our laboratory had initiated the studies of human monoglyceride lipase in 1997, while no information was reported about the MGL human homologue. Using a computer-based approach to align redundant ESTs in the dbEST (The Expressed Sequence Tags database) to search for sequences that contain putative novel open reading frames (ORFs), we delineated several EST containing putative ORFs. We then used the SAGE (Serial Analysis of Gene Expression) database to identify those that would potentially exhibit altered expression in cancers. Using such approaches, we had identified a novel human cDNA predicted to encode a protein with molecular mass of 34 kDa (accession number XM_042586). The PROSITE database (a protein database for functional characterization and annotation, prosite.expasy.org) predicted this novel protein to be a lysophospholipase, we therefore named it as LPL34 (Lysophospholipase 34 kD). The amino acid sequence of LPL34 (human MGL) is shown in Fig. 1. A BLAST comparison of the LPL34 sequence with the non-redundant sequence databases revealed

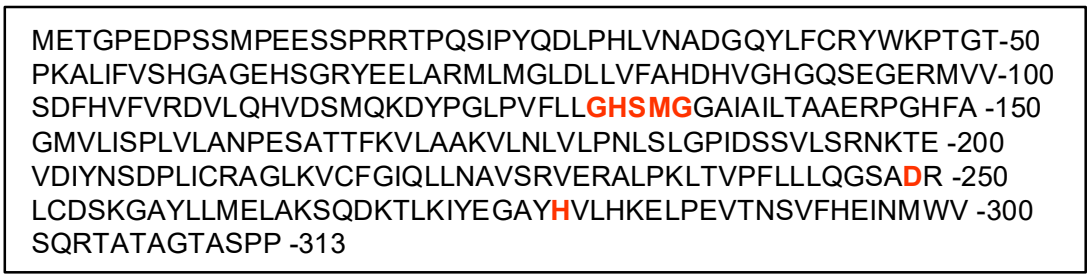

Figure 1. The amino acid sequence of human MGL.

LPL34 to be highly homologous (84% identity) to the murine monoglyceride lipase (MGL) cDNA reported by Karlsson et al. (Karlsson et al., 1997) (accession number AJ001118). Compared to the reported murine MGL, LPL34 (human MGL) has 10 additional amino acids at its N-terminus (Fig. 1). Amino acid residues (Ser122, Asp-239 and His-249) identified as the lipase catalytic triad for murine MGL are conserved in LPL34 corresponding to residues Ser-132, Asp-249 and His-279. Like murine MGL, LPL34 also harbored the conserved lipase motif 'GHSMG' at position 130-134 (Fig. 1). Thus, evidence suggested that LPL34 is the human homologue of murine MGL.

We next investigated whether human MGL cDNA can be expressed and translated into a protein of the expected size. Toward this end, *in vitro* transcription/translation assay was performed on the MGL cDNA; the *in vitro* translated human MGL protein product had a molecular mass of ~34 kD. We also subcloned the human MGL cDNA into mammalian expression vectors and expressed it in human cancer cell lines. Exogenously expressed MGL protein also was ~34 kD in human cells which matched the size of endogenous MGL detected by MGL specific antibody generated in our laboratory.

Further studies determined MGL to be a protein encoded by the MGLL gene localized in mouse chromosome 6 or human chromosome 3q21 (Karlsson et al., 2001; Rajasekaran et al., 2016). It was shown that MGL in mice is widely expressed in multiple tissues including those of the spleen, kidney, stomach, lung, liver, brain, skeletal muscle as well as adipose tissue (Karlsson et al., 2001). Similarly, previous studies of human samples from our laboratory detected MGL mRNA or protein expression in multiple tissues too, including those of the lung, kidney, stomach, brain, skeletal muscle, liver, spleen, small intestine, colon, and prostate (Sun et al., 2013). Therefore, MGL is a lipase

that is not limited to adipose tissue but universally present in a large variety of tissues or cells.

The tumor-suppressive roles of MGL

Our subsequent studies have identified MGL to have important characteristics of tumor suppressor in human cancer (Sun et al., 2013, Liu et al., 2018, Liu et al., 2020). We showed that the expression of MGL was either absent or reduced in multiple human malignancies, particularly in cancers of lung and colon (Sun et al., 2013, Liu et al., 2018, 2019). Overexpression of MGL suppressed colony formation in tumor cell lines (Sun et al., 2013). Purified MGL was found to selectively interact with several purified phospholipids, including phosphatidic acid and phosphoinositol(3,4,5)P3, phosphoinositol(3,5)P2, phosphoinositol(3,4)P2 and several other phosphoinositides (Sun et al., 2013). MGL knockdown resulted in increased Akt phosphorylation whereas overexpression of MGL suppressed Akt phosphorylation (Sun et al., 2013; Liu et al., 2018). Thus, our studies identified MGL to be an important negative regulator for regulating the PI3-K/Akt signaling.

To investigate the role of MGL in tumorigenesis, MGL knockout mice were generated. Our results demonstrated that MGL-deficient ($MGL^{+/-}$, $MGL^{-/-}$) mice exhibited a higher incidence of neoplasia in multiple organs, including the lung, spleen, liver and lymphoid tissues (Liu et al., 2018). Importantly, lung neoplasms were found to be the most common neoplastic changes in the MGL-deficient mice (Liu et al., 2018). MGL deficiency was associated with activation of EGFR, ERK and pro-inflammatory

molecules such as COX-2 and TNF-α (Liu et al., 2018) in the MGL-deficient mouse lung tissues and in human lung cancer cells. Mouse embryonic fibroblasts (MEFs) from MGL-deficient animals showed characteristics of cellular transformation including increased cell proliferation, foci formation and anchorage-independent growth (Liu et al 2018). Our results thus indicate that MGL plays an important role in controlling tumorigenesis in animals.

Our laboratory also investigated whether overexpression of MGL would impair cell survival or even induce cell death. We found that MGL overexpression led to remarkable apoptosis in multiple cancer cell lines such as H1299 lung cancer cells, HeLa cervical cancer cells, and cancer cells extracted from a spontaneously developed tumor from a MGL-knockout mouse (Liu et al., 2020). Our mechanistic studies showed that MGL negatively regulated the X-linked inhibitor of apoptosis protein (XIAP) in multiple cancer cell lines and in mouse tissues including lung and liver, whereas over-expression of XIAP strongly inhibited MGL's ability to cause cell death (Liu et al., 2020). The detailed study of this function of MGL will be elaborated in Chapter 2 of this dissertation.

Similar to our findings regarding the potential tumor-suppressive role of MGL in mouse liver (Liu et al., 2020), another group showed that MGL was expressed in normal hepatocytes but not in hepatocellular carcinoma (HCC) cells (Rajasekaran et al., 2016). Moreover, MGL expression levels were inversely correlated with the expression levels of a pro-tumorigenic protein, staphylococcal nuclease and tudor domain containing 1 (SND1). SND1 was shown to be an interacting protein of MGL and promotes its ubiquitination and proteosomal degradation (Rajasekaran et al., 2016). Mechanistic studies demonstrated that overexpression of MGL inhibited HCC cell proliferation,

blocked cell cycle progression, and suppressed xenograft tumor growth (Rajasekaran et al., 2016). Interestingly, MGL over-expression reduced AKT phosphorylation in HCC cells and this effect is important for MGL's role in the inhibition of cell proliferation and cell cycle progression (Rajasekaran et al., 2016). Furthermore, the inhibition of AKT by MGL is independent of MGL lipase activity (Rajasekaran et al., 2016). Taken together, these findings suggested that MGL was a tumor-suppressor in HCC, which is highly consistent with the findings from our mouse model study (Liu et al., 2020).

Another study investigated the relationship between MGL and Yes-associated protein (YAP) of the Hippo pathway, and identified MGL as a transcriptional target of YAP (Tang and Wang, 2015). The study also found that MGL expression was reduced in head and neck squamous cancer cell lines as compared with that of normal human oral keratinocytes, while overexpression of MGL or the lipase-dead MGL S132A similarly suppressed the anchorage-independent growth of the cancer cell lines (SCC23 and SCC9) (Tang and Wang, 2015). Although MGL overexpression inhibited AKT phosphorylation in SCC23 cells, MGL S132A did not clearly affect AKT phosphorylation, indicating that MGL inhibited cell transformation probably independently of its regulation of AKT (Tang and Wang, 2015). By using MCF10A human normal mammary epithelial cell line, the study showed that YAP was able to promote cell transformation and this effect was inhibited by MGL expression induced by YAP (Tang and Wang, 2015).

The lipase activity of MGL may also be important for its tumor-suppressive function. Although 2-AG exhibits anti-tumor effects as mentioned previously, one study showed that 2-AG levels were higher in low-grade and high-grade glioma tissues as compared with that in non-tumor tissues (Wu et al., 2012). Consistently, MGL lipase activities and

mRNA levels are lower in the glioma tissues when compared with those of the non-tumor tissues (Wu et al., 2012). These results also implicate a tumor-suppressive role of MGL in glioma.

Generally, studies to date support the tumor-suppressive role of MGL in tumorigenesis.

The oncogenic characteristics of MGL

So far, several studies have characterized the function of MGL in the context of tumor formation and progression (Xiang et al., 2018; Nomura et al., 2010; Hu et al., 2014; Tang and Wang, 2015). A number of studies implied that MGL also exhibited oncogenic characteristics.

In one study, it was shown that the serine hydrolase activities of MGL were elevated in aggressive cancer cell lines such as a melanoma cell line C8161, an ovarian cancer cell line SKOV3, and a breast cancer cell line 231MFP, when compared with their non-aggressive counterparts (Nomura et al., 2010). Moreover, in contrast to the situation in normal tissues where MGL generally did not regulate the levels of free fatty acids (FFAs), MGL appeared to be important for the production of FFAs in aggressive cancer cells (Nomura et al., 2010). Knockdown of MGL by shRNA in aggressive cancer cells suppressed cell survival and migration and reduced xenograft tumor growth and its FFA contents, suggesting that MGL activity is critical in maintaining the aggressiveness of cancer cells (Nomura et al., 2010). Interestingly, overexpression of MGL but not MGL lipase-dead mutant, MGL-S122A, in non-aggressive cancer cells increased cellular FFA

levels and promoted cell migration and survival, recapitulating the features of aggressive cancer cells (Nomura et al., 2010). Consistently, the aggressiveness of MGL-depleted cancer cells could be rescued by addition of FFAs such as palmitic acid and stearic acid (Nomura et al., 2010). These findings further indicated that MGL lipase activity played an important role in enhancing the pathogenicity of cancer cells by facilitating cancer cells in generating free fatty acids (FFAs) from stored lipids to promote cell invasion, survival and xenograft tumor growth (Nomura et al., 2010). Surprisingly, the FFAs generated by MGL did not seem to enhance cancer cell pathogenicity via β-oxidation to generate energy for cancer cells. The FFAs generated by MGL are composed of abundant pro-tumorigenic signaling lipids or lipid metabolites including lysophosphatidic acid (LPA) and prostaglandin E2 (PGE2), and their levels were increased in aggressive cancer cells as compared with those of the non-aggressive cancer cells (Nomura et al., 2010). Furthermore, LPA and PGE2 appeared to be important in mediating MGL's role in promoting cancer pathogenicity (Nomura et al., 2010). In addition, 2-AG is a substrate of and hydrolyzed by MGL as mentioned above. Many studies have demonstrated that 2-AG suppressed cancer cell growth in several types of cancers, including pancreatic cancer, prostate cancer, and breast cancer (Carracedo et al., 2006; Nithipatikom et al., 2004; De Petrocellis et al., 1998). Therefore, MGL may promote tumor growth via its capability of hydrolyzing 2-AG. Altogether, these findings suggested that enhanced MGL lipase activity plays an important role in cancer pathogenicity.

The role of MGL in cancer pathogenicity is also described in hepatocellular carcinoma (HCC) (Zhang et al., 2016). Screening of patient samples demonstrated that MGL levels (mRNA and protein) were higher in HCC samples when compared with

normal liver tissues (Zhang et al., 2016). MGL levels were also higher in poorly differentiated HCC samples as compared with well-differentiated ones (Zhang et al., 2016). Tissue microassay and immunohistochemistry results showed that MGL levels were negatively correlated with the degree of HCC differentiation (Zhang et al., 2016). These results implied that MGL might serve as a predictor of the degree of malignancy of HCC (Zhang et al., 2016). Consistently, MGL levels were found to be associated with poor survival of HCC patients (Zhang et al., 2016). In matrigel invasion assays, when HCC cells, SMMC-7721, were treated with MGL inhibitor JZL184 or depleted of MGL with shRNA, cell invasion was significantly reduced, whereas overexpression of MGL increased invasion of SMMC-7721 (Zhang et al., 2016). These results suggest that MGL lipase activity is likely involved in HCC cancer cell invasion. Moreover, JZL184 treatment and shRNA-mediated knockdown of MGL both reduced HCC cell proliferation and increased cell apoptosis, while MGL overexpression promoted the cell proliferation and reduced cell apoptosis (Zhang et al., 2016). The production of the pro-tumorigenic LPA and PGE2 by MGL was also observed in hapatocellular carcinoma cells (Zhang et al., 2016). In xenograft human HCC tumors in mouse, JZL184 treatment and shRNA-mediated knockdown of MGL all decreased tumor growth, whereas MGL overexpression or high fat diet promoted tumor growth (Zhang et al., 2016). Taken together, these findings indicated that the lipase activity of MGL is involved in the formation and progression of HCC and MGL inhibitor may be useful in treating HCC.

In prostate cancer, the lipase activity of MGL is increased in aggressive cancer cells (PC3 and DU145 cells) as compared with less aggressive cancer cells (LNCaP cells), which is similar to the findings from breast, melanoma, and ovarian cancer cells (Nomura

et al., 2011. Chem Biol.). JZL184 treatment or shRNA mediated knockdown of MGL resulted in reduced PC3 cell migration, invasion, and survival (Nomura et al., 2011. Chem Biol.). In the aggressive PC3 cells, MGL seemed to be responsible for the production of lysophosphatidic acid (LPA), phosphatidic acid (PA), and lysophosphatidyl ethanolamines (LPE), which all contribute to cancer aggressiveness by promoting cell migration, invasion and survival (Nomura et al., 2011. Chem Biol.). These results suggest that LPA, PA, and LPE may account for the oncogenic effects of MGL. Furthermore, palmitic acid only partially rescued cell invasion, migration, and survival that were impaired by MGL ablation, potentially through the activities of LPA, PA, and LPE on G-protein coupled receptors (Nomura et al., 2011. Chem Biol.). The cell migration impaired by MGL ablation is restored by treatment with palmitic acid and a cannabinoid receptor type 1 (CB1) antagonist, rimonabant (RIM), while 2-arachidonoylglycerol (2-AG), the substrate of MGL, suppressed PC3 cell migration (Nomura et al., 2011. Chem Biol.). Altogether, these data suggest that MGL promotes prostate cancer pathogenicity at least partially via the production of LPA, PA, and LPE as well as the degradation of 2-AG in prostate cancer (Nomura et al., 2011. Chem Biol.).

The function of MGL in promoting cancer metastases was also demonstrated by another study that identified MGL as an important protein in maintaining the metastatic property of nasopharyngeal carcinoma (NPC) cells (Hu et al., 2014). In NPC cells with high metastatic potential, there were higher levels of MGL mRNA and proteins than those in cells with less metastatic capacity (Hu et al., 2014). Moreover, human NPC tissues also showed higher levels of MGL mRNA than those in non-cancerous tissues (Hu et al., 2014). Exogenous MGL overexpression was able to increase the metastatic

capacity of NPC cells while shRNA mediated MGL depletion reduced NPC cell migration and invasion (Hu et al., 2014). Furthermore, in vivo study in a mouse model of tumor metastasis demonstrated that MGL expression is negatively correlated with NPC tumor cell metastasis (Hu et al., 2014). Mechanistic studies implied that MGL might enhance epithelial-to-mesenchymal transition (EMT) and increase matrixmetalloproteinase (MMP-2) to promote tumor cell metastasis (Hu et al., 2014). Through microarray analysis of aggressive cancer cells versus non-aggressive cancer cells, one study identified a set of genes that were overexpressed in aggressive cancer cells, including a number of genes involved in EMT and genetic markers of cancer stem cells (Nomura et al., 2011. Chem Biol.). Since MGL expression is elevated in aggressive cancer cells, it was thus postulated that the tumorigenic pathways that cause EMT and maintain cancer stem cells might account for the increased expression of MGL (Nomura et al., 2011. Chem Biol.). Overall, the findings from this study suggested that MGL contributed to tumor metastasis, although it did not clarify whether this effect of MGL is associated with its lipase activity.

A recent study showed that MGL was an indicator of high-risk gastrointestinal stromal tumors (GISTs) and a predictor of poor prognosis (Li et al., 2016). The transcriptomic dataset of 32 GISTs underwent clustering analyses and the results indicated that MGL was significantly upregulated in high-risk GISTs as compared with non-high-risk GISTs (Li et al., 2016). Further analyses of MGL mRNA levels in GISTs samples and normal tissues demonstrated that MGL levels were the highest in high-risk GISTs, higher in non-high-risk GISTs, but lowest in normal tissues, implying that MGL promotes GIST progression (Li et al., 2016). MGL overexpression was associated with

clinical or pathological findings that predict poor prognosis such as non-gastric location, larger size of tumors, and increased tumor cell mitosis (Li et al., 2016). Moreover, MGL overexpression was indeed associated with shorter disease-free survival (DFS) (Li et al., 2016). Overall, these findings suggest that MGL may promote GIST progression and lead to poor prognosis in patients.

Aside from its roles in the development of GISTs of the gastrointestinal system, MGL was also reported to be involved in colon cancer formation in a Prdm5LacZ/LacZ;ApcMin mouse model (Galli et al., 2014). Prdm5 is a member of the Prdm family of transcriptional regulators and loss of Prdm5 in ApcMin mouse model significantly increased the number of polyps in the small intestine. Microarray analysis of wild-type and Prdm5 knockout MEFs showed that MGL was negatively regulated by Prdm5 (Galli et al., 2014). ChIP-seq analysis further demonstrated that MGL was a direct target of Prdm5 (Galli et al., 2014). Lastly, Prdm5 protein levels were lower in a large proportion of colon cancer samples as compared with normal tissues, whereas MGL protein levels were higher in colon cancer tissues as compared with normal tissues (Galli et al., 2014). These findings altogether implied that Prdm5 loss in colon epithelium led to increased expression of MGL, which then contributed to colon cancer formation.

Lipase Activity of MGL

Studies of MGL in the brain have shown that MGL is both a membrane-associated enzyme and a cytosolic protein (Blankman et al., 2007; Dinh et al., 2002). The study from our laboratory identified MGL in cancer cells to be a lipid droplet-associated protein localized in the cytoplasm (Sun et al., 2013). It has been shown that

2-monoglycerides are produced via hydrolysis by lipoprotein lipase (LPL) or hormone-sensitive lipase (HSL) from triglycerides, and subsequently monoglyceride is hydrolyzed by MGL, with the final products being free fatty acids and glycerol (Karlsson et al., 2001). In the protein structure of MGL, there is a catalytic triad formed by Ser-122, Asp-239, and His-269 in both mouse and human MGL (isoform of 303 amino acids) that works as the foundation of the lipase activity of MGL (Karlsson et al., 1997; Tyukhtenko et al., 2016). As a lipase, MGL has been shown to play a significant role in energy metabolism. In a mouse model of MGL deficiency (MGL-knockout), it was found that MGL deletion in mice impaired lipolysis, upregulated monoglyceride levels in the adipose tissue and the liver, and attenuated high fat diet-induced insulin resistance (Taschler et al., 2011).

In terms of lipase activity, it seems that the function of MGL is tissue-specific (Dinh et al., 2002). In tissues that commonly metabolize monoacylglycerol (MG) and triacylglycerol (TG) such as those of the small intestine and liver and adipose tissues, MGL is believed to hydrolyze MG derived from TG, releasing fatty acids and glycerol (Dinh et al., 2002; Chon et al., 2007). In the brain, however, 2-arachidonoylglycerol (2-AG) is the major substrate of MGL (Dinh et al., 2002). 2-AG is a special type of monoglyceride and is a member of the endocannabinoid family (Dinh et al., 2002). Of note, many studies of the lipase function of MGL have extensively investigated the role of MGL in the metabolism of endogenous cannabinoids (endocannabinoids) as well as the physiological outcome following the hydrolysis of 2-AG (Dinh et al., 2002). Studies have demonstrated that in the brain tissue, hydrolysis of 2-AG into arachidonic acid (AA) and glycerol is mostly (approximately 85%) catalyzed by MGL while the rest of 2-AG is

hydrolyzed by other enzymes such as ABHD6 and ABHD12 (Dinh et al., 2002; Navia-Paldanius et al., 2012; Blankman et al., 2007). Further studies showed that MGL in the brain played a major role in the generation of AAs from 2-AG and the AAs subsequently served as the precursor substrate for the synthesis of prostaglandins such as Prostaglandin E2 (PGE2) (Nomura et al., 2011. Science.). MGL inhibition by its inhibitor was able to suppress lipopolysaccharide (LPS)-induced neuroinflammatory responses in the mouse brain (Nomura et al., 2011. Science.). Several MGL inhhibitors such as JZL184 and URB602 have been developed to inhibit the lipase activity of MGL (Du et al., 2011; Nomura et al., 2010). One study showed that JZL184 inhibition of MGL lipase activity in cancer cells reduced the production of pro-tumorigenic lysophosphatidic acid (LPA) and prostaglandin E2 (PGE2), and suppressed xenograft tumor growth, implicating the anti-tumor effect of JZL184 (Nomura et al., 2010). Another study demonstrated that URB602 and JZL184 both inhibited NF-κB and COX-2 in hippocampal neurons in culture, implicating the efficacy of MGL inhibitors in treating neuroinflammation, as was also shown by Nomura et al. (Du et al., 2011; Nomura et al., 2011. Science.).

However, the lipase activity of MGL was investigated in cancer cell lines not in human samples. The exact role of MGL as a lipase need to be further investigate in different tumor from patients' samples. The function of MGL inhibitors need to be studied both in vivo and in vitro. The side effects and off-target effects of MGL inhibitors also requires further investigation.

Overall, studies in last few decades have identified, characterized, and elucidated the lipase activity of MGL. Exploring the potential therapeutic values of MGL inhibitors has become a major interest in the field.

Lung cancer

According to the statistics from a new study of global cancer burden, lung cancer is the second most commonly diagnosed cancer and it is still the leading cause of cancer mortality (Sung et al., 2020). Two major types of lung cancer have been described and studied, and they are designated as small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC) (Travis et al., 2015). NSCLC is the most commone type of lung cancer and accounts for more than 85% of lung cancer cases (Chen, 2014; Malhotra et al., 2017). It is further categorized into three subtypes: squamous cell carcinoma (SCC), lung adenocarcinoma (ADC), and large cell carcinoma (Travis et al., 2015). Among all the subtypes of NSCLCs, SCC and ADC are the two predominant types, and approximately 40% of NSCLCs are SCCs and 50% of NSCLCs are classified as ADCs (Chen et al., 2014).

Regarding the causes of lung cancer, the majority (about 90%) of lung cancers are associated with tobacco smoking (Swanton and Govindan, 2016). Tobacco smoke contains various carcinogens and thus cancers related to smoking usually present with high rates of genetic mutations (Gibbons et al., 2017). For example, smoking plays an important role in the formation and development of lung ADCs (Hu and Chen, 2015). Not surprisingly in the case of lung ADCs, a number of common mutations have been reported and they alter the function of certain oncogenes such as KRAS, EGFR, and

PIK3CA as well as tumor suppressor genes such as TP53 and RB1 (Swanton and Govindan, 2016). Although SCC and SCLC cancers exhibit an even stronger association with smoking than ADCs (Khuder 2001), the mutation landscapes in SCC and SCLC cancers are different from that in ADCs (Swanton and Govindan, 2016). For example, PTEN mutation is common in SCCs, accounting for 10.2% of SCC cases whereas it is only detected in 1.7% of ADCs (Heist et al., 2012). However, there are common alterations in genes such as TP53 and RB1 that are detected in SCCs, SCLCs, and ADCs (Swanton and Govindan, 2016). For decades, chemotherapeutic agents such as cisplatin, carboplatin, and pemetrexed are the major therapeutics for the treatment of lung cancer and nowadays they remain critical for the management of lung cancer (Johnson et al, 2014; Lee, 2018). In the era of personalized medicine, molecular-targeted therapy has become a major field of study in medicine and has also been developed for the treatment of lung cancer. The discovery of genetic mutations in lung cancers has led to the development of a variety of targeted therapies. For instance, several generations of EGFR tyrosine kinase inhibitors (TKIs) have been developed to treat patients with non-small cell lung cancer (NSCLC) harboring activating and correspondingly sensitizing mutations of EGFR (Swanton and Govindan, 2016; Le and Gerber, 2019).

Targeted therapies have improved the survival of patients with tumors that express the specific molecular targets, however, they also have their limitations (Lee, 2019). For example, EGFR mutations in NSCLC have been found in 15% to 30% of patients among different populations (Metro and Crinò, 2012). Anaplastic lymphoma kinase (ALK) rearrangement is detected in 3-8% of lung ADCs (Gao et al., 2013; Cerami et al., 2012) and inhibitors of ALK have been developed for the treatment of ADCs harboring

rearrangements of ALK (Awad and Shaw, 2014). Obviously, the frequency of EGFR or ALK alterations are not high and only account for a small portion of ADCs in lung cancer patients, and this significantly limits the use of EGFR or ALK inhibitors. Importantly, previous studies from our laboratory showed that monoglyceride lipase (MGL) expression was either decreased or lost in 65.5% of human lung cancer tissues as compared with matching normal tissues (Sun et al., 2013; Liu et al., 2018). Future studies of the molecular network regulated by MGL may reveal new targets for the treatment of lung cancer and the corresponding targeted therapy may be effective for as much as 65.5% of lung cancer patients.

Apoptosis and tumorigenesis

Apoptosis is a type of programmed cell death that is energy-dependent and genetically determined (Elmore, 2007; Pfeffer and Singh, 2018). It is characterized by distinct morphological characteristics that are different from those of necrosis, another type of cell death (Elmore, 2007). For example, during apoptosis, there is cell shrinkage, the cell membrane is intact, the cytoplasm is retained in apoptotic bodies, and there is no inflammation. As for necrosis, there is cell swelling, the cell membrane is disrupted, the cytoplasm is released, and is usually accompanied by inflammation (Elmore, 2007). Apoptosis is involved in a variety of physiological processes such as embryonic development, normal turnover of cells, immune reactions, and organ atrophy (Elmore, 2007). Apoptosis also plays important roles in pathological processes (Elmore, 2007). For example, deregulated apoptosis has been shown to contribute to the pathogenesis of two

major human disorders, neurodegenerative diseases and cancer (Elmore, 2007; Pfeffer and Singh, 2018).

Studies to date have revealed two major pathways that lead to apoptosis: the mitochondria-related intrinsic pathway and the death receptor-dependent extrinsic pathway (Elmore, 2007). Both pathways require caspases for the induction and execution of cell death (Elmore, 2007; Pfeffer and Singh, 2018). Caspases (cysteine-dependent aspartate-directed proteases) are cysteine proteases that are able to hydrolyze and cleave a target protein at aspartic acid residues (Elmore, 2007). Based on their functions, caspases are classified into categories, the initiator caspases and the executioner caspases (Elmore, 2007). For example, caspase 9 of the intrinsic pathway and caspase 8 of the extrinsic pathway are initiator caspases (Elmore, 2007). The activation of initiator caspases leads to the activation of an executioner caspases such as caspase 3, a shared executioner of the intrinsic and extrinsic pathways that finally results in apoptosis (Elmore, 2007; Tait and Green, 2010). An additional pathway is the perforin/granzyme pathway and it has been shown to be critical for T-cell mediated cytotoxicity (Elmore, 2007). In this pathway, granzyme A is able to induce cell death in a caspase-independent manner whereas granzyme B still requires caspases such as the initiator caspase 10 and the executioner caspase 3 to execute apoptosis (Martinvalet et al., 2005; Elmore, 2007).

The intrinsic pathway involves mitochondria and mitochondrial proteins and is activated by intracellular stimuli such as DNA damage, growth factor deprivation, cytokine withdrawal, failed suppression of apoptosis by antiapoptotic proteins, oxidants, and certain toxins (Elmore, 2007; Pfeffer and Singh, 2018). These signals can lead to mitochondrial outer membrane permeabilization (MOMP), the defining step of the

intrinsic apoptosis pathway, and subsequently mitochondrial proteins such as cytochrome c and second mitochondria-derived activator of caspase (SMAC) from intermembrane space are released into the cytosol (Elmore, 2007; Pfeffer and Singh, 2018). In the cytosol, cytochrome c, apoptotic protease activating factor 1 (Apaf-1), dATP, and pro-caspase 9 form the apoptosome, which converts pro-caspase 9 into active caspase 9 (Elmore, 2007; Pfeffer and Singh, 2018). Capase 9 induces activation of executioner caspases, caspases-3 and caspase-7, which finally lead to cell death (Elmore, 2007; Pfeffer and Singh, 2018).

The extrinsic pathway is primed for activation when death ligands bind to transmembrane receptors such as tumor necrosis factor (TNF) family death receptors (Elmore, 2007; Pfeffer and Singh, 2018). TNF-related apoptosis-inducing ligand (TRAIL), Fas ligand (Fas-L), and tumor necrosis factor (TNF) are common death ligands that can trigger apoptosis (Pfeffer and Singh, 2018). For example, following the binding of tumor necrosis factor TNF-α to its receptor TNFR1, cytoplasmic adaptor proteins including TNF receptor-associated death domain (TRADD), Fas-associated death domain protein (FADD), and receptor interacting protein (RIP) are recruited to the transmembrane receptor to form a death-inducing signaling complex (DISC) together with the initiator caspase 8 (Elmore, 2007). Upon formation of DISC, caspase 8 is activated by an auto-catalytic mechanism, which finally leads to the activation of executioner caspases and apoptosis (Elmore, 2007; Kischkel, 1995; Tait and Green, 2010).

Evasion of apoptosis is a hallmark of cancer while normally apoptosis prevents cancer formation (Elmore, 2007; Pfeffer and Singh, 2018). Cancer cells can either

upregulate anti-apoptotic proteins such as B-cell leukemia/lymphoma-2 (BCL-2) or reduce the expression levels of pro-apoptotic proteins such as BAX to suppress apoptosis (Elmore, 2007; Pfeffer and Singh, 2018). For instance, the tumor suppressor p53 is a typical inducer of apoptosis triggered by DNA damage (Elmore, 2007). In human malignancies loss of p53 or p53 function due to mutations is commonly detected (Elmore, 2007), which supports an important role of apoptosis evasion in tumorigenesis.

Given the importance of apoptosis in the prevention of cancer and its minimal damage to tissues as compared with necrosis, one major goal of cancer therapy is to develop cancer therapeutics to induce apoptosis in cancer cells (Elmore, 2007; Baig et al., 2016). In fact, for the last three decades therapeutic induction of apoptosis by proapoptotic agents has become a mainstay of cancer therapy (Carneiro and El-Deiry, 2020).

The function of XIAP in tumorigenesis

Apoptosis in normal physiology is tightly regulated to maintain tissue homeostasis (Elmore, 2007; Singh et al., 2019). Various proteins have been identified to be important regulators of the apoptosis pathways and are classified as either anti-apoptotic proteins or pro-apoptotic proteins (Singh et al., 2019). Common anti-apoptotic proteins include the Bcl-2 family of proteins such as Bcl-2, Bcl-xL and Mcl-1 (Singh et al., 2019), while Bax, Bak, Bid, Bad, and Bim are typical pro-apoptotic proteins. These protein have been extensively studied in the regulation of the mitochondrial apoptosis pathway (Elmore, 2007; Singh et al., 2019). Another family of proteins, the Inhibitor of apoptosis (IAP) proteins, are also well-established suppressors of apoptosis and they regulate both the

intrinsic and extrinsic pathways (Deveraux and Reed, 1999). Two of its prominent members are X-linked inhibitor of apoptosis protein (XIAP) and survivin (Elmore, 2007). IAPs contain one to three baculovirus IAP repeat (BIR) domain(s) (LaCasse et al., 2008). For example, XIAP has three BIR domains known as BIR1, BIR2, and BIR3 (Abbas R and Larisch, 2020). Additionally, XIAP has a ubiquitin-associated (UBA) domain and a carboxy-terminal RING (really interesting new gene) domain that works as an E3 ligase to mediate protein degradation (LaCasse et al., 2008). Through its BIR1 and BIR2 domains, XIAP inhibits the function of caspases 3 and 7 in the apoptosis pathway (Abbas R and Larisch, 2020). Through its BIR3 domain, XIAP interacts with and inhibits the function of caspase 9 (Schimmer et al, 2006; Abbas R and Larisch, 2020). Furthermore, the anti-apoptotic function of XIAP is also modulated by other proteins such as the mitochondrial proteins Omi/HtrA2 and Smac/DIABLO (Schimmer et al, 2006). During apoptosis, Smac is released from mitochondria into the cytosol where Smac forms a dimer to interact with the BIR2 and BIR3 domains of XIAP, by which Smac prevents XIAP from inhibiting caspase 9 and caspase 3 (Flanagan et al., 2010; LaCasse et al., 2008).

As mentioned above, deregulation of apoptosis is involved in tumorigenesis. It is therefore possible that irregular XIAP function contributes to cancer formation. Indeed, XIAP has been shown to be overexpressed in many tumors (Thompson, 1995; Abbas R and Larisch, 2020). Many studies suggested that overexpression of XIAP was responsible for cancer cell resistance to chemotherapy and was associated with poor prognosis in patients with prostate cancer or acute myeloid leukemia (AML) (Flanagan et al., 2010; Schimmer et al., 2006). Therefore, there has been great interest in the development of

therapeutics that target XIAP for cancer therapy (LaCasse et al., 2008). For example, Smac mimetic compounds (SMCs) have been developed to inhibit XIAP and are tested in clinical trials for cancer therapy either as a single agent or in combination with other therapeutics including checkpoint inhibitors and radiation therapy (LaCasse et al., 2008; Carneiro and El-Deiry, 2020).

Inflammation and tumorigenesis

Physiological inflammation is a normal host response to pathogens, tissue injuries and heals tissues through the interplay between a variety of cytokines and leukocytes and is critical for the maintenance of tissue homeostasis, while abnormal inflammatory responses lead to diseases such as cancer (Coussens and Werb, 2002; Greten and Grivennikov, 2019; Taniguchi and Karin, 2018). In 1863, based on histological observation, Rudolf Virchow suggested a potential link between chronic inflammation and cancer (Balkwill and Mantovani, 2001).

To date, inflammation has been shown by decades of research to play important roles in the development, progression, and treatment of cancer of multiple tissue origins (Coussens and Werb, 2002; Greten and Grivennikov, 2019; Taniguchi and Karin, 2018).

Different types of inflammation are associated with cancer, including chronic inflammation and autoimmunity that precede tumorigenesis, cancer cell-induced inflammation, and inflammation triggered by cancer therapy (Greten and Grivennikov, 2019). Typical cancers associated with chronic inflammation include colorectal cancer, lung cancer, hepatocellular carcinoma, and esophageal cancer (Coussens and Werb, 2002;

Greten and Grivennikov, 2019). A large varitey of cellular or environmental factors contribute to inflammation in cancer, such as inactivation of tumor suppressors, activation of oncogenes, cell death, hypoxia, carcinogenic microbes, and cancer therapeutic agents (Greten and Grivennikov, 2019). Inflammation in cancer can be a double-edged sword in that it may lead to oncogenic mutations, activation of tumor-promoting signaling pathways, tumor-permissive immunosuppression, or induce acquired resistance to the cancer therapeutic agents, but can also trigger anti-tumor immune responses induced by therapy (Sharma and Allison, 2015; Hou, 2017; Srivatsa et al., 2017; Grivennikov et al. 2010; Greten and Grivennikov, 2019).

Multiple mechanisms have been reported regarding tumor-promoting inflammation. It is been shown by a large number of studies that inflammation exerts its tumor-promoting effects at all stages of tumorigenesis (Grivennikov et al. 2010; Greten and Grivennikov, 2019). Inflammation may cause genetic mutations, epigenetic modifications, promote cell proliferation, enhance cell survival, and contribute to immunosuppression during the formation of a tumor (Grivennikov et al. 2010; Greten and Grivennikov, 2019). In addition, inflammation is often accompanied by the elevated production of certain cytokines such as interleukin-1β (IL-1) and tumor necrosis factor-α (TNFα), increased expression of matrix metalloproteinases MMP2 and MMP9, and enhanced activities of Nuclear factor kappa B (NF-κB) and STAT3 (Signal Transducer And Activator Of Transcription 3), by which inflammation promotes angiogenesis, EMT (epithelial to mesenchymal transition), and tumor invasion, finally leading to cancer metastasis (Grivennikov et al. 2010; Greten and Grivennikov, 2019).

Notably, TNF and COX-2 are both target genes of NF-κB and both are involved in tumor-promoting inflammation (Bassères and Baldwin, 2006; Taniguchi and Karin, 2018). Tumor necrosis factor (TNF) is a cytokine that plays important roles in both host immunity and inflammation (Wajant, 2009). In fact, TNF is identified to be a major player in inflammation and inhibitors of TNF have been developed for the treatment of inflammatory diseases such as rheumatoid arthritis (Balkwill, 2009). Interestingly, in the context of cancer, TNF is also a key player in tumor-promoting inflammation (Balkwill, 2009). But the role of TNF in tumor development and progression depends heavily on the cellular and environmental contexts, and TNF shows both pro-tumor and anti-tumor activities in a context-dependent manner (Balkwill, 2009). Early studies of TNF showed that TNF caused tumor necrosis and shrinkage in both patients and mouse models (Balkwill, 2009). Later studies identified TNF as a ligand that can induce apoptosis through TNF receptors and their downstream apoptosis signaling pathways (Balkwill, 2009;Wang and Lin, 2008). These findings altogether support the anti-tumor activities of TNF. On the other hand, TNF signaling induces inflammation and promotes cell survival via transcription factors including AP1 and NF-κB (Balkwill, 2009; Wang and Lin, 2008). Moreover, TNF in the tumor microenvironment was shown to cause DNA damage, thus contributing to tumor initiation (Balkwill, 2009). Other studies also demonstrated that TNF promotes cell proliferation, migration, angiogenesis, immune evasion, and resistance to chemotherapy (Balkwill, 2009; Wang and Lin, 2008). These discoveries, therefore, revealed the pro-tumor activities of TNF.

Cyclooxygenase-2 (COX-2) is an enzyme that catalyzes the metabolism of arachidonic acid (AA) to produce prostaglandins (PGs) (Liu et al., 2015). COX-2 is not

only a common mediator of inflammatory responses, but also plays important roles in tumorigenesis (Liu et al., 2015; Bassères and Baldwin, 2006; Taniguchi and Karin, 2018). Multiple studies have shown that COX-2 levels are high in tumors of different tissue origins including tumors of the colon, breast, pancreas, liver, and lung (Liu et al., 2015). Mechanistically, COX-2 is able to inhibit apoptosis, enhance cell migration, induce angiogenesis, and promote tumor immune evasion so that it is involved in all stages of tumorigenesis (Gupta and DuBois, 2001; Liu et al., 2015). Selective COX-2 inhibitors have been shown to significantly reduce the risks of colon cancer, lung cancer, breast cancer, and prostate cancer, and therefore they are promising candidate agents for cancer prevention (Göbel et al., 2014; Liu et al., 2015).

In line with the tumor-promoting roles of inflammation, anti-inflammatory drugs including COX-2 inhibitors and aspirin have shown effects in cancer prevention (Gupta and Dubois, 2001; Gierach et al., 2008). Interestingly, Canakinumab (ACZ885, Ilaris), a human anti-IL-1β monoclonal antibody that inhibits IL-1β, was shown to significantly reduce the incidence of lung cancer in a clinical trial of 10,061 patients (Ridkeret al., 2017).

IκBα and NF-κB in tumorigenesis

Given the close association of inflammation with cancer, studies have shown that molecular components of the inflammatory signaling pathways are commonly involved in cancer development and progression (Coussens and Werb, 2002; Greten and Grivennikov, 2019). A major one of them is Nuclear factor kappa B (NF-κB) (Greten and Grivennikov, 2019; Taniguchi and Karin, 2018). Nuclear factor-kappa B (NF-κB) is a

family of transcription factors including c-Rel, RelA (p65), RelB, NF-κB1 (p105) and NF-κB2 (p100), and they or their proteolytically processed products undergo dimerization to form homodimers or heterodimers to function as either transcriptional repressors or activators to regulate transcription of target genes (Hayden and Ghosh, 2012; Hoesel and Schmid, 2013; Savinova et al., 2009).

There are two major pathways leading to NF-κB activation, the canonical pathway (also known as the classical pathway) and the non-canonical pathway (also known as the alternative pathway) (Oeckinghaus et al., 2009; Taniguchi and Karin, 2018). Extracellular stimuli are the most common triggers of NF-κB signaling, and the typical stimuli include cytokines, bacterial or viral infections, and antigen-receptor interactions (Oeckinghaus et al., 2009; Oeckinghaus et al., 2011). In addition, genotoxic stresses can also induce NF-κB activation (Oeckinghaus et al., 2009).

In the canonical pathway, when there is no stimulation, inhibitory IκB (inhibitor of NF-κB) proteins bind with NF-κB dimers and sequester NF-κB in the cytoplasm, thus blocking its nuclear translocation (Oeckinghaus et al., 2011). The pathway is activated by extracellular stimuli such as the inflammatory cytokine, tumor necrosis factor (TNF), or by the bacterial lipopolysaccharide (LPS), when they are bound to their respective receptors (Oeckinghaus et al., 2011; PMID: 22302935). Upon receptor-ligand binding, adaptor proteins are recruited to the cytoplasmic regions of the receptors, where they can activate downstream IκB kinase (IKK) (Napetschnig and Wu, 2013). Activated IKK phosphorylates IκB, leading to its ubiquitination and proteasomal degradation, and thus NF-κB dimers are released from the cytoplasmic IκB-NF-κB complex and translocated to the nucleus, where NF-κB functions as a transcription factor to transactivate target genes

(Oeckinghaus et al., 2011; Hayden and Ghosh, 2012; Napetschnig and Wu, 2013). IκB is also present in the nucleus, where it can prevent NF-κB dimers from binding to DNA and even facilitate the shuttling of the NF-κB dimers back to the cytoplasm (Birbach et al., 2002; Huang et al., 2000). Interestingly, nuclear export of NF-κB by IκB is dominant in cells under resting conditions, and therefore NF-κB is localized predominantly in the cytoplasm with a basal transcriptional activity in the nucleus while the cytoplasmic NF-κB can be readily activated upon signal stimulation (Birbach et al., 2002; Huang et al., 2000).

The non-canonical pathway is activated by extracellular stimuli such as the TNF family cytokines, CD40L and lymphotoxin-β (LT-β), when they are bound to their corresponding receptors respectively (Oeckinghaus et al., 2011). In a similar way as in the canonical pathway, the ligand-receptor interaction leads to activation of IKK, and the activated IKK subsequently phosphorylates p100 in a dimer with RelB and p100 is then processed into the smaller NF-κB subunit, p52, which finally forms the transcriptionally active p52-RelB NF-κB complexes (Oeckinghaus et al., 2011; Savinova et al., 2009).

Through its target genes, NF-κB plays important roles in inflammatory responses, immune responses, and the regulation of cell proliferation and survival through their target genes (Oeckinghaus and Ghosh, 2009; Taniguchi and Karin, 2018). To date, it is well-established that NF-κB contributes to tumorigenesis via its versatility of functions and it has been shown that they are activated not only in cancer cells but also in the tumor microenvironment (Oeckinghaus and Ghosh, 2009; Taniguchi and Karin, 2018). More specifically, NF-κB activation promotes cell proliferation and survival but inhibits

apoptosis, mediates tumor-promoting inflammation and epithelial/mesenchymal transition, induces immunosuppression, angiogenesis and cancer metastasis, thereby contributing to its significant role in both cancer development and progression (Taniguchi and Karin, 2018; Bassères and Baldwin, 2006). For example, NF-κB induces expression of cyclin D1 and c-myc to promote cell proliferation and expression of the well-established anti-apoptotic proteins such as X-linked inhibitor of apoptosis protein (XIAP), B-cell lymphoma 2 (Bcl-2), and B-cell lymphoma-extra large (Bcl-xL) to inhibit apoptosis (Bassères and Baldwin, 2006; Taniguchi and Karin, 2018). NF-κB mediates tumor-promoting inflammation through its target genes encoding the pro-inflammatory cytokines such as TNF, IL-1, and interleukin-8 (IL-8), as well as the pro-inflammatory enzyme such as cyclooxygenase 2 (COX-2) (Bassères and Baldwin, 2006; Taniguchi and Karin, 2018).

NF-κB activation is involved in a large variety of cancers studied to date and the typical examples include gastrointestinal cancers, liver cancer, lung cancer, pancreatic cancer, prostate cancer, Hodgkin's lymphoma, B-cell lymphoma, and multiple myeloma (Bassères and Baldwin, 2006; Taniguchi and Karin, 2018). Of particular interest to our study of lung cancer, a previous study has shown that NF-κB siganling is required for tumor formation in a mouse model of lung adenocarcinoma (Meylan et al., 2009). NF-κB thus has become an important target for cancer therapy and and also for the study of cancer drug resistance (Taniguchi and Karin, 2018; Hoesel and Schmid, 2013). Although NF-κB inhibitors are not considered as ideal individual agents for cancer treatment due to their effects on cancer immunity, NF-κB inhibitors in combination with

chemotherapeutics have shown promising results in multiple types of cancers (Hoesel and Schmid, 2013).

In our recent studies, we found that MGL interacts with and inhibits XIAP, implying that MGL is an endogenous inhibitor of XIAP. We further showed that such function of MGL is important for its induction of cancer cell apoptosis and may therefore contribute to MGL's tumor suppressive role, at least in lung tumorigenesis. Moreover, our newest findings suggest that MGL plays an important role in the modulation of tumor-promoting inflammation via its inhibitory regulation of NF-κB signaling pathway. Overall, our studies demonstrated a tumor-suppressive role of MGL in tumorigenesis and multiple mechanisms have been elucidated for such a role of MGL.

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