

REVIEW ARTICLE

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Roles of aminoacyl-tRNA synthetase-interacting multi-functional proteins in physiology and cancer

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Abstract

Aminoacyl-tRNA synthetases (ARSs) are an important class of enzymes with an evolutionarily conserved mechanism for protein synthesis. In higher eukaryotic systems, eight ARSs and three ARS-interacting multi-functional proteins (AIMPs) form a multi-tRNA synthetase complex (MSC), which seems to contribute to cellular homeostasis. Of these, AIMPs are generally considered as non-enzyme factors, playing a scaffolding role during MSC assembly. Although the functions of AIMPs are not fully understood, increasing evidence indicates that these scaffold proteins usually exert tumor-suppressive activities. In addition, endothelial monocyte-activating polypeptide II (EMAP II), as a cleavage product of AIMP1, and AIMP2-DX2, as a splice variant of AIMP2 lacking exon 2, also have a pivotal role in regulating tumorigenesis. In this review, we summarize the biological functions of AIMP1, EMAP II, AIMP2, AIMP2-DX2, and AIMP3. Also, we systematically introduce their emerging roles in cancer, aiming to provide new ideas for the treatment of cancer.

Facts

AIMPs have various biological functions in addition to their roles as scaffolds in the MSC.

AIMPs and their variants are related to the occurrence and development of cancer.

Understanding of the molecular mechanisms linking AIMPs to cancer can contribute to identify new potential antitumoral strategies.

Open questions

Does the dysregulation of AIMPs in cancer affect the structure and function of the MSC?

What is the molecular mechanism by which AIMPs

regulate tumorigenesis?

Is there potential for practical clinical applications based on findings concerning AIMPs in the context of cancer?

Introduction

Aminoacyl-tRNA synthetases (ARSs) are essential enzymes that participate in protein synthesis by catalyzing the activation of amino acids and linking them to their cognate transfer RNAs (tRNAs). In mammals, ARSs usually exist in free form or in the form of a multi-tRNA synthetase complex (MSC), and the latter consists of eight ARSs and three non-enzymatic ARS-interacting multi-functional proteins (AIMP1/p43, AIMP2/p38, and AIMP3/p18)¹. Among them, AIMPs are generally considered as auxiliary proteins and play a role in scaffolding during MSC assembly². In fact, AIMPs have several appended domains or motifs, which are involved in MSC formation and mediation of new functions¹ (Fig. 1a). Meanwhile, AIMPs are closely linked with each other, and each of them has its preferable interacting ARSs in the MSC^{3–6}. For example, X-ray crystallography confirmed that a ternary subcomplex consisting of aspartyl-tRNA synthetase (DRS), glutamyl-prolyl-tRNA synthetase

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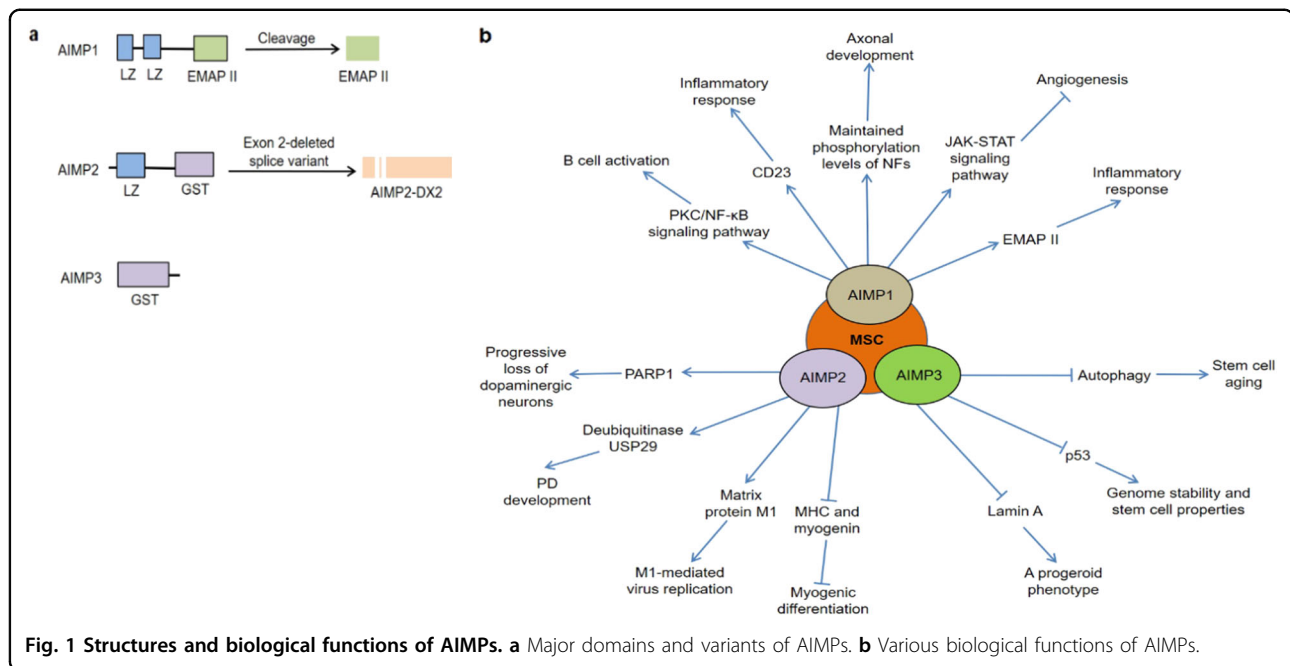
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Edited by: F. Pentimalli

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(EPRS) and AIMP2 provided a key architecture in the MSC⁷. In this subcomplex, AIMP2 interacted with EPRS mainly through the heterodimerization of glutathione *S*-transferase (GST) domains, while DRS bound to AIMP2 by hydrogen bonds between the $\alpha 7$ - $\beta 9$ loop of DRS and the $\beta 2$ - $\alpha 2$ loop of AIMP2_{GST}. Cho et al. found that four components, methionyl-tRNA synthetase (MRS), EPRS, AIMP2, and AIMP3, were assembled via a heterotetrameric complex structure of the GST domains in the human MSC⁸. Moreover, the full-length AIMP1 bound to AIMP3, and the N-terminus of AIMP1 bound to the GST-L domain of EPRS in the MSC⁹.

Interestingly, accumulating evidence has identified that AIMPs participate in various physiological and pathological processes as multifaceted molecules^{10–13}. It was reported that the downregulation of AIMP1 enhanced transforming growth factor- β (TGF- β) signal by inducing the phosphorylation of Smad family member 2/3 (Smad2/3), which in turn promoted the chondrogenic potential of dedifferentiated/degenerated chondrocytes¹⁴. Furthermore, patients with a homozygous c.105C>A (p.Tyr35-Ter) mutation in AIMP2 showed microcephaly, seizures, mental retardation, and spastic quadriplegia¹⁵. Recent studies found that AIMP3 could maintain genomic integrity through the DNA repair process, and the adult mice with AIMP3 deletion developed an acute radiation syndrome-like phenotype¹⁶. Strikingly, AIMPs are also related to tumorigenesis^{17–19}, which suggested that studying the additional functions of AIMPs in the context of cancer could expand our understanding of tumorigenesis. Here, we not only summarize the biological functions of AIMP1, EMAP II, AIMP2, AIMP2-DX2, and

AIMP3, but also focus on their emerging roles in regulating tumorigenesis, suggesting that their thorough study may provide new insights into cancer treatment.

Biological functions of AIMPs

Apart from their role as scaffolds in the MSC, AIMPs also have a variety of biological functions^{20–23}. Notably, these non-canonical functions are closely related to immune regulation, nervous system functions, angiogenesis, viral replication, and genome stability (Fig. 1b).

AIMPs and immune regulation

AIMPs work as regulators or signaling molecules in some immune and inflammatory processes^{24–26}. A previous study found that mammalian cells could specifically secrete the full-length AIMP1 without an apoptosis signal. In human monocytic THP-1 cells, AIMP1 could activate mitogen-activated protein kinase (MAPK) and nuclear factor- κ B (NF- κ B) and induce the expression of multiple cytokines as well as chemokines, such as tumor necrosis factor (TNF), interleukin 8 (IL-8), monocyte chemotactic protein 1 (MCP-1) and macrophage inflammatory protein-1 α (MIP-1 α), which were generally regarded as the main factors inducing atherosclerosis²⁷. Importantly, AIMP1 was highly expressed in the foam cells of atherosclerotic lesions, indicating that it might promote the development of atherosclerosis by inducing cytokines and chemokines. CD23 (Fc ϵ R2) was thought to be a functional receptor molecule for AIMP1, which mediated the inflammatory response induced by AIMP1²⁸. During this process, AIMP1 bound to CD23 and subsequently induced TNF- α secretion by activating extracellular

signal-regulated kinase 1/2 (ERK1/2) in THP-1 cells and peripheral blood mononuclear cells (PBMCs). Notably, a neutralizing antibody MHM6 inhibited the secretion of TNF- α induced by AIMP1 via competing with IgE for binding to CD23, suggesting that the interaction between AIMP1 and CD23 in monocytes might play an important role in autoimmune diseases. Recently, Kim et al. demonstrated that AIMP1 inhibited T cell receptor (TCR)-mediated CD4 T cell activation and proliferation²⁹. AIMP1 weakened the TCR signal by interfering with lipid raft aggregation and thus reduced the phosphorylation of phospholipase C γ (PLC γ) and phosphatidylinositol 3-hydroxy kinase (PI3K) in CD4 T cells. At the same time, AIMP1 specifically enhanced the differentiation of regulatory T (Treg) cells, but had no effect on the differentiation of T helper type 1 (Th1), Th2, and Th17 cells.

EMAP II was first discovered to be secreted by tumor cells and could induce acute inflammatory response *in vivo*³⁰. Subsequent research showed that AIMP1 was the precursor of EMAP II, which was released after AIMP1 cleavage^{31,32}. Lee et al. revealed that EMAP II promoted the development of bronchopulmonary dysplasia (BPD) in mice by recruiting macrophages to aggravate the inflammatory state³³. By further confirming the transcription characteristics of macrophages exposed to EMAP II, researchers found that the unique transcription profile in response to EMAP II was mainly mediated by janus kinase (JAK)-signal transducer and activator of transcription 3 (STAT3), providing a direction for the study of EMAP II-mediated inflammation³⁴. Furthermore, TCR affinity controlled the differentiation process by regulating the AIMP3, IL-2R α -chain (CD25) and guanylate binding protein 2 (Gbp2) in naive T cells³⁵. Specifically, low TCR affinity induced the expression of Gbp2, thereby promoting T follicular helper (Tfh) cell differentiation, while high TCR affinity induced the expression of AIMP3 and CD25, thereby promoting non-Tfh cell formation.

AIMPs and nervous system functions

Pathogenic mutations in AIMP1 have been reported to be associated with neurological diseases, such as neurodegenerative disease, pontocerebellar hypoplasia, and intellectual disability^{36–38}. For example, a homozygous c.917A>G (p.Asp306Gly) mutation in AIMP1 caused severe neurodegenerative phenotypes, including developmental delays, epilepsy and progressive microcephaly³⁹. Meanwhile, magnetic resonance imaging (MRI) showed that the neuroimaging features were callosal atrophy and T2 hyperintensity in the superficial white matter, as well as preserved myelination in the periventricular and deep white matter structures. Of note, AIMP1-deficient mice showed axon degeneration in motor neurons, defects of neuromuscular junctions, motor dysfunction and

muscular atrophy⁴⁰. AIMP1 was mainly expressed in central neurons and specifically interacted with the rod domain of neurofilament-light subunit (NF-L). Moreover, AIMP1 was a negative regulator of NF phosphorylation, and its overexpression or depletion could change the phosphorylation level of NFs, leading to the NF network disassembly. Recently, Xu et al. discovered that the N terminus of AIMP1 was responsible for the binding to its C terminus and arginyl-tRNA synthetase (RARS), and it also colocalized to the NF-L subunit protein⁴¹. These findings suggest that AIMP1 plays an important role in NF assembly and axon maintenance, which provides a new idea for exploring the pathogenesis of neurological diseases.

Interestingly, AIMP2 was a Parkin substrate⁴². In the dopaminergic neuroblastoma-derived SH-SY5Y cell line, Parkin promoted the ubiquitylation and degradation of AIMP2. Importantly, the overexpression of Parkin significantly protected SH-SY5Y cells from AIMP2-induced cell death. Lee et al. showed that AIMP2 accumulation overactivated poly(ADP-ribose) polymerase-1 (PARP1), resulting in the PAR accumulation and progressive loss of dopaminergic neurons, suggesting that AIMP2-induced parthanatos contributed to dopaminergic cell death, and that PARP1 inhibitors might be used to delay the progression of Parkinson's disease (PD)⁴³. Conspicuously, vacuolar protein sorting-associated protein 35 (VPS35) prevented AIMP2-mediated PARP1 activation and cell death by facilitating lysosomal degradation of AIMP2, suggesting that VPS35 might be a potential target for relieving PD⁴⁴. AIMP2 transcriptionally upregulated deubiquitinase ubiquitin-specific peptidase 29 (USP29), resulting in the accumulation of 160 kDa myb-binding protein (MYBBP1A) in PD⁴⁵. The expression of USP29 and MYBBP1A was upregulated in the Parkin knockout SH-SY5Y cells and the ventral midbrain of AIMP2 transgenic mice, suggesting that MYBBP1A might contribute to the development of PD.

Other biological functions

A previous study by Park et al. demonstrated that AIMP1 played a dose-dependent biphasic role in angiogenesis⁴⁶. Low concentrations of AIMP1 activated matrix metalloproteinase 9 (MMP9) through ERK, leading to the migration of endothelial cells. Conversely, high concentrations of AIMP1 activated c-Jun N-terminal kinase (JNK), thereby inducing the apoptosis of endothelial cells. Mechanistically, the JAK-STAT signaling pathway mediated the inhibitory effect of AIMP1 on angiogenesis⁴⁷. Furthermore, many studies have shown that EMAP II is an effective antiangiogenic cytokine^{48,49}. In myocardial infarction mice treated with EMAP II antibody, researchers found upregulated angiogenesis-related biomarkers and increased endothelial cell, suggesting that

EMAP II blockade improved cardiac function by inducing angiogenesis⁵⁰.

In influenza A virus (IAV)-infected cells, the virus NS2 protein protected host AIMP2 from ubiquitin-mediated degradation⁵¹. Subsequently, the accumulated AIMP2 promoted the conversion from ubiquitination to SUMOylation of matrix protein M1, thereby promoting M1-mediated virus replication. This finding suggests that AIMP2 plays an important role in IAV infection and may serve as a potential target for the treatment of influenza. Furthermore, researchers also discovered that AIMPs were associated with DNA damage. Liu et al. found that the rs12199241 of AIMP3 was significantly related to the levels of DNA damage in Chinese population⁵². Analogously, AIMP3 depletion in mouse embryonic stem cells blocked double-strand break repair, which resulted in the accumulation of DNA damage and genome instability⁵³. In addition, AIMPs were also involved in other biological processes, such as glucose homeostasis, liver fibrosis, myogenic differentiation, and aging^{54–58}.

Roles of AIMPs in cancer

Cancer is a serious threat to human health and life and is rapidly becoming a major global health burden. A growing number of reports have described the association between AIMPs and cancer, suggesting the potential significance of AIMPs in cancer biology.

AIMP1 and cancer

Lee et al. observed that AIMP1 had significant anti-tumor activity in a xenograft mouse model⁵⁹. The expression of AIMP1, AIMP2, and AIMP3 was down-regulated in gastric and colorectal cancer, which might result in their inactivation of tumor suppressor functions and tumor development⁶⁰. Moreover, RARS could regulate the secretion of AIMP1 in HeLa and MCF7 cell lines⁶¹. In laryngeal squamous cell carcinoma (LSCC) tissues, AIMP1 and leukotriene A4 hydrolase (LTA4H) were upregulated and promoted the proliferation, migration, and invasion of LSCC cells⁶². Importantly, AIMP1 and LTA4H bound to fascin actin-bundling protein 1 (FSCN1), suggesting that their interaction might promote the progress of LSCC.

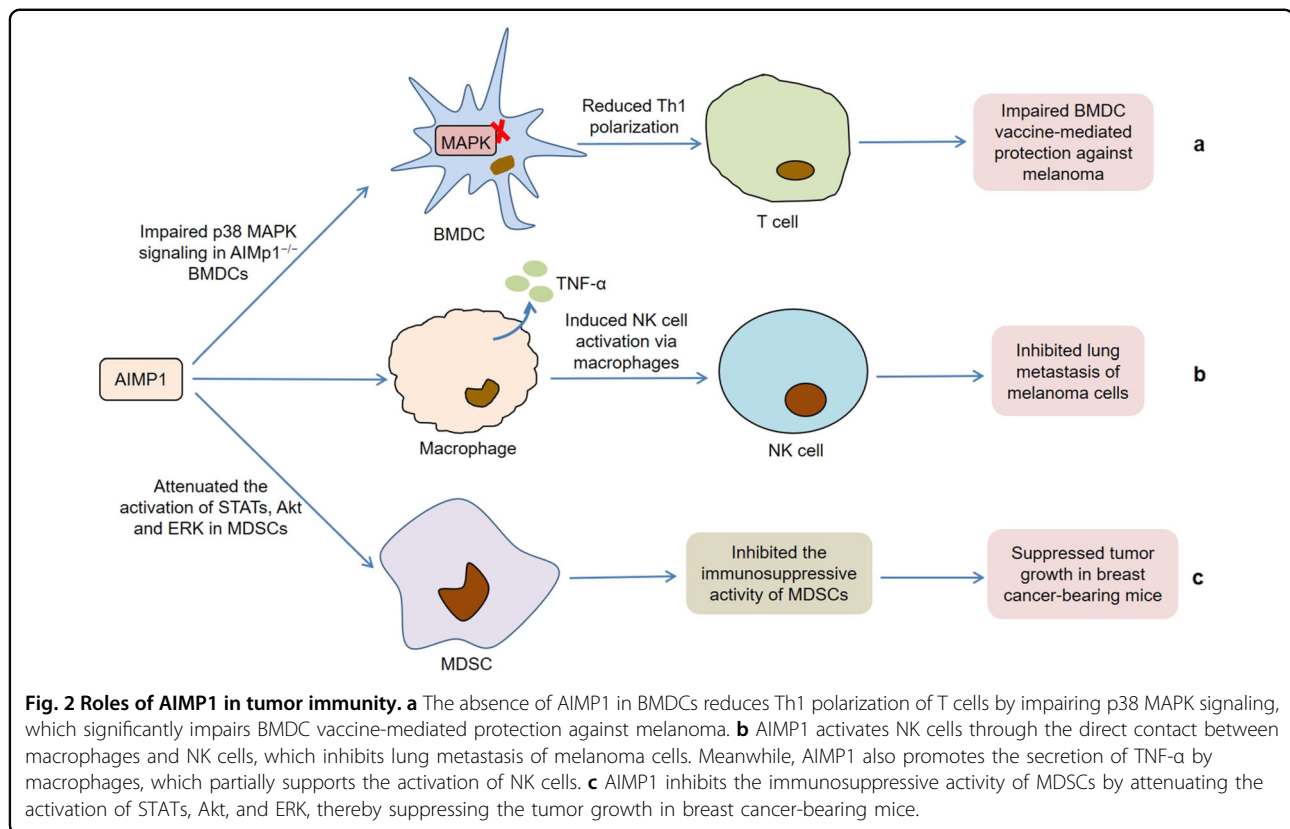
Particularly, AIMP1 plays an important regulatory role in tumor immunity. Based on the abundant immunophenotype in glioblastoma (GBM), Cheng et al. identified eight immune-related genes with prognostic value in GBM⁶³. Of these, AIMP1, forkhead box O3 (FOXO3) and zinc finger and BTB domain containing 16 (ZBTB16) were defined as protective with HR < 1, whereas IL-6, IL-10, chemokine ligand 18 (CCL18), Fc fragment of IgG receptor IIb (FCGR2B) and MMP9 were defined as risky with HR > 1. Meaningfully, the researchers developed a local immune-related risk signature from these genes to

distinguish cases as high or low risk of unfavorable prognosis.

Moreover, the absence of AIMP1 in bone marrow-derived dendritic cells (BMDCs) reduced downstream Th1 polarization of T cells by impairing p38 MAPK signaling, which significantly weakened BMDC vaccine-mediated protection against melanoma⁶⁴. Meanwhile, The Cancer Genome Atlas (TCGA) database analysis showed that the expression of AIMP1 in nearly 9000 primary tumor samples was highly correlated with long-term survival. These results indicated that AIMP1 was critical for effective antitumor immunity. Kim et al. supported that AIMP1 activated natural killer (NK) cells through macrophages, which significantly inhibited lung metastasis of melanoma cells in vivo⁶⁵. In this process, the direct contact between macrophages and NK cells was necessary for AIMP1-induced NK cell activation. AIMP1 also significantly promoted the secretion of TNF- α by macrophages, which partially supported the activation of NK cells. Interestingly, AIMP1 reduced the population of myeloid-derived suppressor cells (MDSCs) in the spleens and primary tumor sites of breast tumor-bearing mice and inhibited the expansion of MDSCs in tumor-conditioned media⁶⁶. In addition, AIMP1 not only negatively regulated the inhibitory activity of MDSCs by reducing the production of IL-6, nitric oxide (NO), and arginase-1 (Arg-1), but also effectively attenuated the ability of MDSCs to suppress T cell proliferation and induce Treg cell differentiation in vivo. Further research discovered that the negative regulation of MDSC functions by AIMP1 might be related to the weakened activation of STATs, protein kinase B (Akt) and ERK. Collectively, these findings indicate that AIMP1 actively participates in tumor immunity through regulating various physiological processes, such as Th1 polarization, NK cell activity, and MDSC functions (Fig. 2).

EMAP II and cancer

Previous research found that EMAP II was a tumor-suppressive cytokine with antiangiogenic effects, which inhibited the primary and metastatic tumor growth and facilitated apoptosis in growing capillary endothelial cells⁶⁷. Low-dose EMAP II inhibited tumor growth by inducing defective autophagy and G2/M arrest in glioblastoma stem cells (GSCs)⁶⁸. Mechanistically, EMAP II reduced the expression of phosphorylated PI3K and Akt with concomitant induction of FoxO1 activation. The specific knockout of FoxO1 greatly reduced the induction of autophagy and G2/M arrest, suggesting that the PI3K/Akt/FoxO1 axis was involved in the anticancer effect of EMAP II in GSCs. Li et al. demonstrated that EMAP II inhibited the viability, migration, and tube formation of GBM-induced endothelial cells (GECs) by inducing autophagy, thereby inhibiting GBM-induced

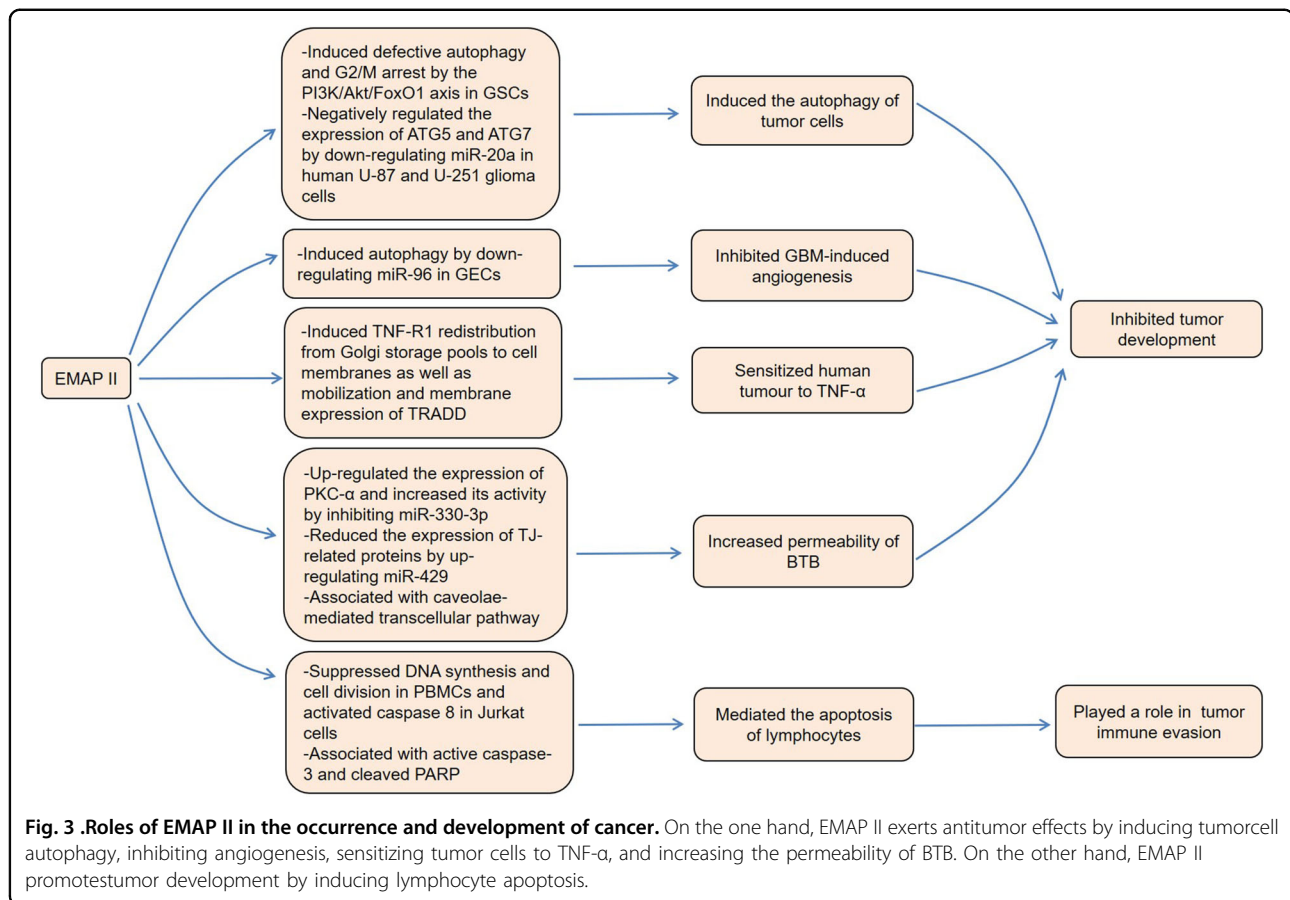


angiogenesis⁶⁹. GECs treated with EMAP II showed upregulated expression of microtubule-associated protein-1 light chain-3 (LC3) and sequestosome 1 (p62/SQSTM1) and blockage of PI3K/Akt/mammalian target of rapamycin (mTOR) pathway. At the mechanistic level, EMAP II downregulated the expression of miR-96, which upregulated the expression of LC3 and p62/SQSTM1 by directly targeting unfolded protein response (UPR)-related proteins, such as glucose-regulated protein 78 (GRP78), eukaryotic translation initiation factor 2 alpha (eIF2 α) and C/EBP homologous protein (CHOP). Analogously, low-dose EMAP II induced autophagy by downregulating the expression of miR-20a in human U-87 and U-251 glioma cells⁷⁰. In this process, miR-20a negatively regulated the expression of autophagy-related 5 (ATG5) and ATG7 by directly targeting their 3'-UTR, thereby activating the autophagy pathway.

In addition, EMAP II sensitized human melanoma to systemic TNF- α in vivo⁷¹. Mechanistic investigations found that the expression of TNF-R1 protein was not increased in human endothelial cells treated with EMAP II, but instead was redistributed from Golgi storage pools to cell membranes⁷². Meanwhile, EMAP II induced the membrane expression and mobilization of TNF-R1-associated death domain (TRADD) protein. Intriguingly, EMAP II was associated with the permeability of blood-

tumor barrier (BTB)^{73–75}. Liu et al. observed that EMAP II upregulated the expression of protein kinase C- α (PKC- α) and increased its activity by inhibiting the expression of miR-330-3p, resulting in a decreased expression of tight junction (TJ)-related proteins including zonulae occludens-1 (ZO-1), occludin and claudin-5, as well as an increased permeability of BTB⁷⁶. MiR-429 also mediated the effects of EMAP II on the permeability of BTB⁷⁷. Specifically, EMAP II significantly upregulated the expression of miR-429, which not only inhibited the expression of ZO-1 and occludin by directly interacting with them, but also reduced the expression of TJ-related proteins by downregulating the expression and phosphorylation of p70 ribosomal protein S6 kinase (p70S6K). Furthermore, caveolae-mediated transcellular pathway was involved in the increased permeability of BTB induced by EMAP II in C6 glioma rats⁷⁸.

Interestingly, in addition to the various antitumor effects described above, EMAP II is also associated with immune escape by tumor cells. Recombinant EMAP II suppressed DNA synthesis and cell division in PBMCs and induced apoptosis in PBMCs and Jurkat cells⁷⁹. Consistently, native EMAP II expressed on the surface of HT29 cells could activate caspase 8 in Jurkat cells, which led to their apoptosis. Youssef et al. pointed out that colorectal cancer cells secreted EMAP II under hypoxic



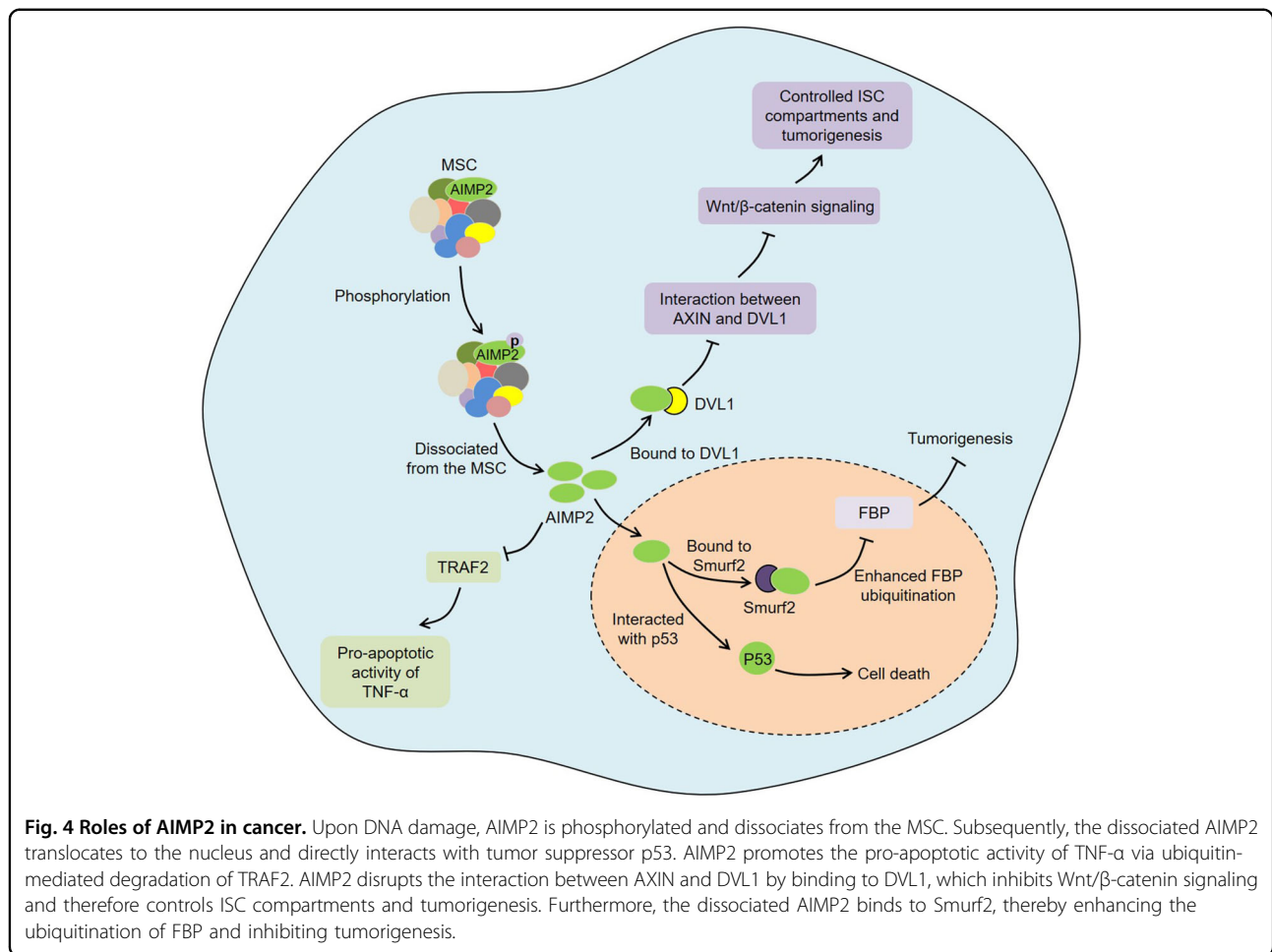
conditions, which mediated the apoptosis of tumor-infiltrating lymphocytes induced by hypoxia⁸⁰. In conclusion, EMAP II not only exerts antitumor effects by inducing autophagy of tumor cells, inhibiting angiogenesis, sensitizing tumor cells to TNF- α , and increasing the permeability of BTB, but also promotes the development of cancer by inducing lymphocyte apoptosis (Fig. 3).

AIMP2 and cancer

It is reported that AIMP2 usually shows tumor-suppressive activities (Fig. 4). A previous study by Choi et al. supported that the decreased AIMP2 levels in heterozygous AIMP2 mice provided greater sensitivity to multiple tumor formations, suggesting that AIMP2 could serve as a haploinsufficient tumor suppressor⁸¹. AIMP2-deficient cells were resistant to DNA damage-induced cell death, while the overexpression of AIMP2 enhanced the sensitivity to apoptosis⁸². Upon DNA damage, AIMP2 was phosphorylated by JNK and dissociated from the MSC. Subsequently, the dissociated AIMP2 translocated to the nucleus and directly interacted with tumor suppressor p53, thereby inhibiting murine double minute 2 (MDM2)-mediated ubiquitination and degradation of

p53. These findings indicate that AIMP2 can regulate cell death through p53. It is well known that TNF- α is closely related to tumorigenesis^{83,84}. TNF- α induced cell death was decreased in AIMP2-deficient cells⁸⁵. Conversely, exogenous supplementation of AIMP2 enhanced the apoptotic sensitivity to TNF- α . Further studies shown that AIMP2 promoted the ubiquitin-dependent degradation of TNF receptor-associated factor 2 (TRAF2) by enhancing the recruitment of the E3 ligase c-IAP1 to TRAF2, thus mediating the pro-apoptotic activity of TNF- α . This finding suggests that AIMP2 may be involved in tumor development by regulating the TNF- α signaling pathway.

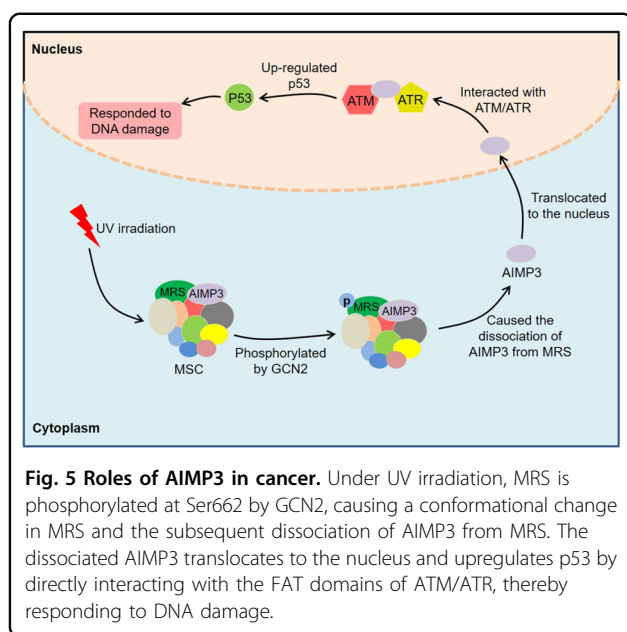
Hemizygous deletion of AIMP2 increased the formation of adenoma in *Apc*^{Min/+} mice and resulted in the proliferation of intestinal epithelial cells (IECs) in crypts and expansion of intestinal stem cell (ISC) compartments⁸⁶. Further research found that AIMP2 disrupted the interaction between axis inhibition protein (AXIN) and Dishevelled-1 (DVL1) by binding to DVL1, which inhibited Wnt/ β -catenin signaling and therefore controlled ISC compartments and tumorigenesis. Moreover, TGF- β induced AIMP2 expression and promoted its translocation to the nucleus, thereby participating in lung cell



differentiation⁸⁷. Mechanistically, the AIMP2 in the nucleus interacted with FUSE-binding protein (FBP), which stimulated the ubiquitination and degradation of FBP, leading to the downregulation of c-Myc. Another study discovered that upon TGF- β stimulation, AIMP2 was phosphorylated at S156 site by p38 MAPK and then dissociated from the MSC in HeLa cells⁸⁸. The dissociated AIMP2 translocated to the nucleus and bound to Smad ubiquitin regulatory factor 2 (Smurf2), thereby enhancing the ubiquitination of FBP and inhibiting tumor formation. Notably, the S156A mutant in AIMP2 that inhibited its nuclear interaction with Smurf2 promoted tumorigenesis in vivo. Zhong et al. demonstrated that the RARS-mitotic arrest deficient-like 1 (MAD1L1) fusion protein interacted with AIMP2 to increase the expression of FBP, thereby promoting the occupation of the c-Myc promoter by FBP and subsequently inducing cancer stem cell (CSC)-like properties⁸⁹. These data suggest that the development of drugs targeting the FBP/c-Myc axis via combinatorial therapy may be beneficial for certain types of cancer patients.

AIMP2-DX2 and cancer

AIMP2-DX2, as a splice variant of AIMP2 lacking exon 2, was highly expressed in human lung cancer cells, and the ratio of AIMP2-DX2 to normal AIMP2 was increased with cancer progression⁹⁰. Endogenous AIMP2-DX2 impaired the pro-apoptotic activity of AIMP2 through the competitive binding to p53 in lung cancer A549 cells. Interestingly, transgenic mice expressing AIMP2-DX2 showed increased sensitivity to lung tumorigenesis compared to the wild type counterpart. Jung et al. discovered that lung cancer patients with high AIMP2-DX2/AIMP2 autoantibody ratio had significantly shorter overall survival than those with low ratio, suggesting that AIMP2-DX2 levels were related to the clinical outcome of lung cancer⁹¹. Moreover, AIMP2-DX2 was highly expressed in chemoresistant ovarian cancer⁹². AIMP2-DX2 reduced the pro-apoptotic activity of TNF- α by competitively inhibiting the binding of AIMP2 to TRAF2, thereby contributing to the chemoresistance of ovarian cancer. Heat shock protein 70 (HSP70) was positively correlated with AIMP2-DX2 in lung cancer patient tissues⁹³.



Importantly, HSP70 could block the Seven in absentia homolog 1 (Siah1) binding and ubiquitination of AIMP2-DX2 by specifically recognizing and stabilizing AIMP2-DX2, leading to an increase in AIMP2-DX2 levels. X-ray crystallography and NMR analysis revealed that HSP70 bound to the amino (N)-terminal flexible region and glutathione S-transferase domain of AIMP2-DX2 through its substrate-binding domain. Furthermore, AIMP2-DX2 promoted the proliferation, migration, and invasion of nasopharyngeal carcinoma (NPC) cells by upregulating MMP-2 and MMP-9⁹⁴. In short, AIMP2-DX2 can not only serve as a potential biomarker for lung cancer, but also participate in tumorigenesis. Interestingly, the downregulation of AIMP2-DX2 expression by shRNA suppressed the epidermal growth factor receptor (EGFR)/MAPK signaling pathway, thereby inhibiting glucose uptake and cancer cell growth⁹⁵. Therefore, suppressing the expression of AIMP2-DX2 may be an effective strategy for treating cancer.

AIMP3 and cancer

As with AIMP2, AIMP3 was also a haploinsufficient tumor suppressor⁹⁶. AIMP3 upregulated p53 by directly interacting with the FAT domains of ataxia telangiectasia-mutated/ATM and Rad 3-related (ATM/ATR), thereby responding to DNA damage. Kim et al. observed several mutations of AIMP3 in chronic myeloid leukemia (CML) patients⁹⁷. Of these, the mutations at Ser⁸⁷, Val⁹⁸, and Arg¹⁴⁴ blocked the interaction between AIMP3 and ATM, suggesting that these residues had important functions for p53 activation. Generally, AIMP3 and MRS interacted through the GST-homology domains in the MSC⁹⁸. Under UV irradiation, MRS was phosphorylated at Ser662

by general control nonrepressed-2 (GCN2), causing a conformational change in MRS and the subsequent dissociation of AIMP3 from MRS. The dissociated AIMP3 translocated to the nucleus, where it participated in the DNA damage response. Hepatitis B virus X protein (HBx) activated the lncRNA highly upregulated in liver cancer (HULC) promoter through cAMP-responsive element-binding protein (CREB), thereby upregulating HULC expression in liver cancer HepG2 cells⁹⁹. It was worth noting that the upregulated HULC promoted the proliferation of liver cancer cells by downregulating AIMP3. These results indicate that AIMP3 works as an important signaling molecule in tumorigenesis (Fig. 5).

AIMP3 expression was reduced in muscle-invasive bladder cancer (MIBC), resulting in impaired Tp53 transactivity and genomic instability¹⁰⁰. Significantly, the reduction of AIMP3 increased the resistance of cancer cells to ionizing radiation. At the same time, AIMP3 expression predicted relapse and overall survival after radiotherapy, indicating that it could serve as a potential clinical biomarker for MIBC. Intriguingly, higher AIMP3 expression was associated with better survival in gastric and colon adenocarcinoma, but with poor survival in breast, lung, and liver cancers¹⁰¹. Therefore, more in-depth research is needed to explore the relationship between AIMP3 and survival outcomes across cancer types.

AIMPs and potential therapeutic interventions

Meaningfully, several studies have focused on the potential clinical applications of AIMP3 in cancer treatment. After 6 days of intravenous injection of recombinant AIMP1 in a mouse xenograft model bearing human stomach cancer cells, the tumor volume and weight decreased significantly¹⁰². The cells exhibiting an active cell cycle progression were reduced in tumor tissues of AIMP1-treated mice, and the blood levels of TNF- α and IL-1 β were increased, indicating that AIMP1 might play an anti-tumor role by inducing tumor inhibiting cytokines. Furthermore, pharmacokinetic studies of a single intravenous injection in rats found that AIMP1 showed a low clearance and a low volume of distribution, and its half-life was 6 min.

Interestingly, low-dose EMAP II induced Bcl-2/adeno-virus E1B 19 kDa protein-interacting protein 3 (BNIP3)-mediated mitophagy by downregulating miR-24-3p, thereby enhancing the temozolomide cytotoxicity of GSCs¹⁰³. Mice treated simultaneously with EMAP II, temozolomide and miR-24-3p inhibitor showed the smallest tumors and the longest survival rates, suggesting that the combined use of EMAP II and temozolomide might be a new approach for the treatment of glioma. Similarly, Awasthi et al. demonstrated that EMAP II enhanced the antitumor effects of sorafenib and

Table 1 Roles of AIMPs in cancer.

AIMPs	Cancer type	Cell/tissue type	Effects	Mechanisms	References
AIMP1	LSCC	Hep2 and TU-177	Promoted the proliferation, migration and invasion of LSCC cells	AIMP1 and LTA4H were upregulated in LSCC tissues and interacted with FSCN1	62
	GBM	Tumor tissue samples were obtained from glioma patients	Defined as an immune-related gene with prognostic value in GBM		63
	Melanoma	B16F10 and B16F0-OVA	Impaired BMDC vaccine-mediated protection against melanoma	The absence of AIMP1 in BMDCs reduced downstream Th1 polarization by impairing p38 MAPK signaling	64
	Melanoma	B16F1	Inhibited lung metastasis of melanoma cells	Activated NK cells through macrophages	65
	Breast cancer	4T1	Suppressed tumor growth in breast cancer-bearing mice	Negatively regulated MDSC functions by weakening the activation of STATs, Akt and ERK	66
	Stomach cancer	MKN45	The cells exhibiting an active cell cycle progression were reduced in AIMP1-treated mice	Induced tumor-suppressing cytokines, such as TNF- α and IL-1 β	102
EMAP II	Lung cancer and breast cancer	LLC and MDA-MB 468	Inhibited the primary and metastatic tumor growth and facilitated apoptosis in growing capillary endothelial cells		67
	GBM	U87-MG	Inhibited tumor growth	Inducing defective autophagy and G2/M arrest in GSCs by PI3K/Akt/FoxO1	68
	GBM	U87	Inhibited GBM-induced angiogenesis	Induced autophagy by downregulating miR-96 in GECs	69
	GBM	U-87 and U-251	Inhibited the viability, migration and invasion of glioma cells	Negatively regulated the expression of ATG5 and ATG7 by downregulating miR-20a	70
	Melanoma	Pmel, 883, Smel and T286	Sensitized human melanoma to TNF- α	Induced TNF-R1 redistribution from Golgi storage pools to cell membranes and mobilization and membrane expression of TRADD	71,72
	GBM	U87	Increased permeability of BTB	Upregulated the expression of PKC- α and increased its activity by inhibiting miR-330-3p	76
	GBM	U87	Increased permeability of BTB	Reduced the expression of TJ-related proteins by upregulating miR-429	77
	GBM	C6	Increased permeability of BTB	Associated with caveolae-mediated transcellular pathway	78
	Colorectal cancer	HT29, DLD-1, LS513 and HCT-15	Induced apoptosis in PBMCs and Jurkat cells	Suppressed DNA synthesis and cell division in PBMCs and activated caspase 8 in Jurkat cells	79
	Colorectal cancer	DLD-1 and HT29	Mediated the apoptosis of tumor-infiltrating lymphocytes induced by hypoxia	Associated with active caspase-3 and cleaved PARP	80
AIMP2		NCI-H157, A549 and NCI-H460	Functioned as a proapoptotic factor in response to DNA damage	Interacted with tumor suppressor p53	82
		HeLa	Mediated the pro-apoptotic activity of TNF- α	Promoted the ubiquitin-dependent degradation of TRAF2	85

Table 1 continued

AIMPs	Cancer type	Cell/tissue type	Effects	Mechanisms	References
	Colorectal cancer	HCT116 and HeLa A549	Controlled ISC compartments and tumorigenesis Participated in lung cell differentiation and suppressed proliferation of the epithelial carcinoma cells	Inhibited Wnt/ β -catenin signaling Downregulated FBP and c-Myc	86 87
		WI-26, 293T and HeLa	Inhibited tumor formation	Bound to Smurf2 and thus enhanced the ubiquitination of FBP	88
	NPC	CNE2, HK1 and S26	Induced CSC-like properties	RARS-MAD1L1 fusion protein interacted with AIMP2 to increase the expression of FBP	89
AIMP2-DX2	Lung cancer	A549, NCI-H460, H322 and H157	Increased susceptibility to carcinogen-induced lung tumorigenesis	AIMP2-DX2 impaired the pro-apoptotic activity of AIMP2 through binding to p53	90
	Ovarian cancer	A2780, SKOV3 and HeyA8	Contributed to the chemoresistance of ovarian cancer	Reduced the pro-apoptotic activity of TNF- α by competitively inhibiting the binding of AIMP2 to TRAF2	92
	Lung cancer	H522, H1435, H460, etc.	Led to an increase in AIMP2-DX2 levels	HSP70 blocked the Siah1 binding and ubiquitination of AIMP2-DX2	93
	NPC	5-8F, CNE-1 and CNE-2Z	Promoted the proliferation, migration and invasion of NPC cells	AIMP2-DX2 upregulated MMP-2 and MMP-9	94
	Lung cancer	H460	Inhibited the growth of cancer cells	Targeted and replaced the AIMP2-DX2 RNA with a new transcript by a trans-splicing ribozyme	108
	Lung cancer	NCI-H23, NCI-H322, NCI-H358 and NCI-H460	Reduced the viability of small cell lung cancer cells	SLC8050 inhibited the interaction between AIMP2-DX2 and p14/ARF	109
AIMP3		HCT116, A549 and H460	The AIMP3 heterozygous mice showed high susceptibility to tumors	Upregulated p53 by directly interacting with ATM/ATR, thereby responding to DNA damage	96,97
		HeLa	The dissociated AIMP3 translocated to the nucleus and participated in the DNA damage response	MRS was phosphorylated by GCN2, causing a conformational change in MRS and the subsequent dissociation of AIMP3 from MRS	98
	Liver cancer	HepG2, Hep3B and PLC/PRF/5	HULC promoted the proliferation of liver cancer cells	Downregulated the expression of AIMP3	99
	MIBC	T24, 253J, RT112 and RT4	The reduction of AIMP3 increased the resistance of cancer cells to ionizing radiation	Associated with impaired Tp53 transactivity and genomic instability	100

AIMP1 ARS-interacting multi-functional protein 1, TNF- α tumor necrosis factor- α , IL-1 β interleukin 1 β , RARS arginyl-tRNA synthetase, LSCC laryngeal squamous cell carcinoma, LTA4H leukotriene A4 hydrolase, FSCN1 fascin actin-binding protein 1, GBM glioblastoma, BMDC bone marrow-derived dendritic cell, MAPK mitogen-activated protein kinase, MK natural killer, MDSC myeloid-derived suppressor cell, STATs signal transducers and activators of transcription, Akt protein kinase B, ERK extracellular signal-regulated kinase, GSCs glioblastoma stem cells, PI3K phosphatidylinositol 3-hydroxy kinase, FoxO1 forkhead box O1, GECs GBM-induced endothelial cells, ATG5 autophagy-related 5, TRADD TNF-R1-associated death domain, BTB blood-tumor barrier, PKC- α protein kinase C- α , Tl tight junction, PBMCs peripheral blood mononuclear cells, PAPP Poly(ADP-ribose) polymerase, TRAF2 TNF receptor associated factor 2, ISC, intestinal stem cell, Smurf2 Smad ubiquitin regulatory factor 2, FBP FUSE-binding protein, CSC cancer stem cell, MAD1L1 mitotic arrest deficient-like 1, AIMP2-DX2 AIMP2 lacking exon 2, HSP70 heat shock protein 70, Siah1 seven in absentia homolog 1, NPC nasopharyngeal carcinoma, MMP matrix metalloproteinase, ATM ataxia telangiectasia-mutated, ATR ATM and Rad 3-related, MRS methionyl-tRNA synthetase, GCN2 general control nonrepressed-2, HULC highly upregulated in liver cancer, MIBC muscle-invasive bladder cancer.

gemcitabine in pancreatic ductal adenocarcinoma (PDAC)¹⁰⁴. Compared to the control group, the combination therapy significantly improved animal survival. Notably, the serum EMAP II levels in patients with non-small cell lung cancer were significantly higher than in healthy subjects, and high serum EMAP II levels were associated with shorter survival, indicating that EMAP II could serve as a new biomarker for non-small cell lung cancer¹⁰⁵.

In addition, many studies have attempted to suppress tumor development by targeting AIMP2-DX2^{106,107}. Won et al. effectively inhibited the growth of cancer cells by designing a trans-splicing ribozyme that targeted and replaced the AIMP2-DX2 RNA with a new transcript¹⁰⁸. This ribozyme performed the RNA replacement by a high-fidelity trans-splicing reaction with the targeted residue of AIMP2-DX2 RNA, but did not work on normal AIMP2 transcript. AIMP2-DX2 eliminated oncogene-induced cell death and aging by binding to and inhibiting p14/ARF, thereby promoting tumorigenesis¹⁰⁹. Conspicuously, a novel compound, SLCB050, could reduce the viability of small cell lung cancer cells by inhibiting the interaction between AIMP2-DX2 and p14/ARF. Another inhibitor, BC-DXI-495, specifically bound to AIMP2-DX2 and blocked its interaction with HSP70, thus exerting an anti-tumor activity⁹³. Furthermore, the label-free molecular probe based on G-quadruplex and strand displacement could sensitively and selectively detect AIMP2-DX2, which might be used for early diagnosis and monitoring the progression of relevant cancer¹¹⁰.

Conclusion and future perspective

Since the MSC plays an important role in protein synthesis, it is important to understand its structural features and the physiological functions of its components. Of these, AIMPs are generally considered as auxiliary proteins and play a scaffolding role during MSC assembly. In addition, AIMPs also participate in a spectrum of biological processes, including immune regulation, nervous system functions, angiogenesis, and genome stability, which are considered unexpected because AIMPs are classified as housekeeping proteins. Interestingly, most of the non-canonical functions are more or less related to tumorigenesis. In fact, AIMPs and their variants do play a vital role in tumor biology (Table 1). Specifically, AIMPs usually exert tumor-suppressive activities, while AIMP2-DX2 is involved in the development of cancer. Furthermore, certain AIMPs are also regarded as biomarkers for cancer prognosis. Therefore, the study of AIMPs in the context of cancer will be a promising field. However, more molecular mechanisms are needed to further clarify the relationship between AIMPs and cancer.

Indeed, as another component of the MSC, certain ARSs were also involved in tumorigenesis^{111,112}. Genetic variants in several ARS genes have been reported to be associated with breast cancer risk in Chinese population¹¹³. Recently, Zirin et al. found that ARSs were important mediators of Myc growth control in *Drosophila*, and their inhibitors killed human cells overexpressing Myc, suggesting that ARSs might serve as targets for treating Myc-driven cancers¹¹⁴. AIMP2s are also emerging as closely related to cancer biology, and taking them into consideration will lead to a better understanding of tumorigenesis and contribute to the treatment of malignant tumors.

Acknowledgements

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 21 January 2020 Revised: 3 July 2020 Accepted: 6 July 2020

Published online: 24 July 2020

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