**Name of Journal: *World Journal of Biological Chemistry***

**ESPS Manuscript NO: 31747**

**Manuscript Type: Editorial**

**Common therapeutic target for both cancer and obesity**

Chang YH. Methionine aminopeptidase-2 and angiogenesis

**Yie-Hwa Chang**

**Yie-Hwa Chang,** Edward A. Doisy Department of Biochemistry and Molecular Biology, Doisy Research Center, St. Louis University Medical School, St. Louis, MO 63104, United States

**Author contributions:** Chang YH solely contributed to this paper.

**Conflict-of-interest statement:** None.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Invited manuscript

**Correspondence to: Yie-Hwa Chang, Associate Professor** of Edward A. Doisy Department of Biochemistry and Molecular Biology, Doisy Research Center, St. Louis University Medical School, 1100 S. Grand Blvd., St. Louis, MO 63104, United States. changyh@slu.edu

**Telephone:** +1-314-9779256

**Fax:** +1-314-9972422

**Received:** December 5, 2016

**Peer-review started:** December 6, 2016

**First decision:** January 16, 2017

**Revised:** February 22, 2017

**Accepted:** March 12, 2017

**Article in press:**

**Published online:**

**Abstract**

Obesity and cancer are two interrelated conditions of high epidemiological need, with studies showing that obesity is responsible for nearly 25% of the relative contribution to cancer incidence. Given the connection between these conditions, a drug that can operate on both obesity and cancer is highly desirable. Such a drug is accomplishable through the development of potent anti-angiogenesis agents due to the shared underlying role of angiogenesis in the development of both diseases. Prior research has demonstrated a key role of type-2 methionine aminopeptidase (MetAP2) for angiogenesis, which has led to the development of numerous of novel inhibitors. Several irreversible MetAP2 inhibitors have entered clinical trials without great success. Though this lack of success could be attributed to off-target adverse effects, the underlying causes remain unclear. More promising reversible inhibitors have been recently developed with excellent pre-clinical results. However, due to insufficient knowledge of the biological functions of N-terminal protein processing, it is hard to predict whether these novel inhibitors would successfully pass clinical trials and thereby benefit cancer and obesity patients. Significantly more efforts are needed to advance our understanding of the regulation of methionine aminopeptidases and the processes by which they govern the function of proteins.

**Key words:** Methionine aminopeptidase; Angiogenesis; Cancer; Obesity; Diabetes; Protein processing; Protein stability; Protein maturation; Protein modification

**© The Author(s) 2017.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** There were approximately 14 million new cancer cases worldwide each year and more than half of the population in the developed countries are overweight or obese. Obesity is responsible for nearly 25% of the relative contribution to cancer incidence, which ranks second only to tobacco use. It would be, therefore, highly desirable to have drugs that work for both cancer and obesity. In this article, the biological function of a common therapeutic target, methionine aminopeptidase-2, and the status of some of its inhibitors in pre-clinical and clinical trials for cancer and/or obesity were discussed.

Chang YH.Common therapeutic target for both cancer and obesity. *World J Biol Chem* 2017; In press

**METHIONINE AMINOPEPTIDASE-2 IS A COMMON THERAPEUTIC TARGET FOR BOTH CANCER AND OBESITY**

According to the most recent data from the World Health Organization, there are approximately 14 million new cancer cases and 8.2 million cancer-related deaths worldwide each year. The number of new cancer cases is expected to rise by about 70% over the next 20 years[1]. The financial costs of cancer in the United States per year are approximately $263 billion. Moreover, more than half of the population in the developed countries are overweight or obese[2]. The prevalence in children in all developed countries is about 15%. It has been predicted that, if current trends continue, the number of children under 5 who are overweight or obese would rise to 70 million worldwide by 2025. Obesity is commonly associated with numerous diseases, including type 2 diabetes mellitus, hypertension, stroke, gallbladder disease, dyslipidemia, sleep apnea, hepatic steatosis endometrial disorder, and cancer[3-5]. Obesity is responsible for nearly 25% of the relative contribution to cancer incidence, which ranks second only to tobacco use[1]. Significance evidence shows that both neoplastic and non-neoplastic tissue growth are dependent on angiogenesis. Furthermore, it is well established that cancer mortality is mainly due to metastatic tumors, and that angiogenesis is required for tumor metastasis[6]. This suggests that anti-angiogenesis agents could provide a novel therapeutic option for the prevention and treatment of both human obesity and cancer. One major molecular target for developing anti-angiogenesis agents is type-2 methionine aminopeptidase (MetAP2)[7-13]. This molecular target provides a crucial link of the functions of methionine aminopeptidases to both cancer and obesity.

**TWO DISTINCT TYPES OF EUKARYOTIC METHIONINE AMINOPEPTIDASES ARE RIBOSOME-ASSOCIATED METALLOPROTEASES AND EMETAP2 IS BI-FUNCTIONAL**

Methionine aminopeptidases (MetAPs) are responsible for the removal of the initiator methionine (iMet) during protein synthesis. The iMet is removed when the second residue is small and uncharged (G, A, P, S, C, T, V), a function that has been evolutionarily conserved across microbes and humans[14-23]. There are two types of methionine aminopeptidases in eukaryotic cells[20-26]. These two types of MetAPs share low sequence similarity. However, they are both metalloproteases and belong to the “pita-bread” (or M24) protease family with a pseudo two-fold axis of symmetry in the catalytic site and a metal ion binding site located at the interfaces between domains[27]. In addition, each eukaryotic MetAP (eMetAP) contains a unique N-terminal domain linking each MetAP to a distinct site near the exit of the nascent polypeptide chains[23,28-31]. The eukaryotic type 1 MetAP (eMetAP1) contains two zinc finger-like motifs that are involved in ribosomal association[28-31]. It has been demonstrated recently that nascent polypeptide-associated complex (NAC) and eMetAP1, like signal recognition particle (SRP), contacts the ribosome *via* Rpl25/35, the universal adaptor site of the ribosome. It has also been shown that NAC prevents antagonism between SRP and eMetAP1 binding[32]. The eukaryotic type 2 MetAP2 (eMetAP2), on the other hand, contains polycharged Lys-rich block(s) that play a role in its ribosome association[31]. This unique N-terminal motif is also associated with POEP (protection of eIF2α phosphorylation) activity[33] which can prevent the phosphorylation of the alpha subunit of eukaryotic initiation factor 2 (eIF2α). This function of eMetAP2 connects the processing of iMet with the regulation of the initiation of protein synthesis. However, the interplay between these two functions is yet to be discovered.

**METHIONINE AMINOPEPTIDASES ARE ESSENTIAL FOR CELL GROWTH, WHICH GOVERN THE FUNCTION AND STABILITY OF CERTAIN PROTEINS**

MetAP activity is essential for cell growth, as demonstrated by several deletion experiments, including the deletion of a single MetAP in *Escherichia coli* and *Salmonella typhimurium* and the deletion of both MetAP1 and MetAP2 in *Saccharomyces cerevisiae*[25], all of which result in lethality. Failure to remove initiator methionine may therefore have several detrimental effects on protein function. This could be due to the importance of methionine removal for subsequent N-terminal modifications, including N-myristoylation and N-acetylation, the lack of which may alter protein stability, localization, or functional interactions. Multiple examples have demonstrated that inappropriate retention of initiator methionine can, in some circumstances, result directly in decreased protein stability[34,35]. Another possible cause is that the removal of initiator methionine may be required to expose a mature N-terminal residue involved in catalysis. An example is the case of some N-terminal nucleophile aminotransferases, which have a nucleophilic N-terminal cysteine[36]. It would be very interesting to find out whether there are other classes of enzymes whose functions are controlled by the removal of iMet.

**THE METAP2 IS A COMMON THERAPEUTIC TARGET FOR CANCER *VIA* ANTI-ANGIOGENESIS**

Angiogenesis, the process of the formation of new blood vessels, is known to be important for the pathogenesis of several major human diseases. These include rheumatoid arthritis, diabetic retinopathy, and cancer[37-39]. It has been firmly demonstrated that angiogenesis is essential for tumor growth and metastasis[40,41]. Fumagillin has been demonstrated as a potent angiogenesis inhibitor in vivo[42-46]. One of the fumagillin analogs, TNP-470, was shown to be a much more potent inhibitor of tumor progression than fumagillin in multiple animal models, and entered clinical practice in 1992[42,47]. Despite encouraging preliminary findings against several cancers[48-50], further progress of this compound in clinical trials was hampered in part by its toxicity to central nervous system (CNS) and rapid clearance.

To understand the molecular basis of angiogenesis inhibition by fumagillin, ovalin, and TNP-470, eMetAP2 was identified as a common molecular target for this class of inhibitors[7-13]. These findings indicate that eMetAP2 plays a role in human endothelial cell proliferation by blocking the G1 phase entry of the cell cycle[51], thereby becoming a potential therapeutic target for cancer. In addition, it was found that the His-231 residue in the active site was irreversibly modified by fumagillin spiroepoxide[9-12]. In the fumagillin/MetAP2 complex, the hexenyl chain of fumagillin functionally mimics Met thioether. Following this discovery, PPI-2458, a novel fumagillin derivative was developed. This compound differs from fumagillin in that the polyolefinic chain, which extends out of the active site, is replaced by a carbamoyl-linked D-valinamide moiety[52,53]. PPI-2458 has shown efficacy in rodent models for melanoma[54], non-Hodgkin lymphoma[55], and arthritis[49,56-58]. The safety and tolerance of PPI-2458 in patients with non-Hodgkin’s lymphoma and solid tumors was examined in phase I clinical trials between 2004 and 2007[49]. All metabolites retained significant MetAP2 inhibitory and antiproliferative activities. It has also been demonstrated that there is a good correlation between highly efficient inhibition of circulating MetAP2 and rapid metabolite formation, confirming the importance of active metabolites in the efficacy of PPI-2458. Unfortunately, no further reports could be identified after this Phase I study report in 2009. To increase the oral bioavailability and specificity of TNP-470, as well as decrease its toxicity, TNP-470 was conjugated into a polymeric delivery system N-(2-hydroxypropyl) methacrylamide (HPMA) copolymer with a Gly-Phe-Leu-Gly linker. This conjugate is believed to selectively accumulate in tumor vessels due to an enhanced permeability and retention (EPR) effect[59]. However, though a multi-institutional phase II study of TNP-470 in patients with metastatic renal carcinoma revealed its manageable toxicity, it does not lead to any significant objective responses[60].

A more potent fumagillin derivative, CKD-732 (also known as ZGN-433 or beloranib), exhibits a 2-fold increase in sensitivity than TNP-470 and a 1000-fold increase in selectivity than fumagillin for vascular endothelial cells[61]. Based on the anti-angiogenic activity of CKD-732, a Phase I study plus XELOX was conducted in metastatic colorectal cancer (mCRC) patients who have been previously treated with irinotecan-based chemotherapy. In this study, a very promising clinical benefit rate of 100% was observed with a small number of participants. Unfortunately, there have been no further reports after the publication in 2012. It would be highly beneficial to have Phase II data that may further elucidate the value of eMetAP2 as a target for cancer therapy.

**THE METAP2 IS ALSO A THERAPEUTIC TARGET FOR OBESITY *VIA* ANTI-ANGIOGENESIS**

Worldwide prevalence of obesity has nearly doubled since 1980. Recently, inhibition of pathological angiogenesis in adipose tissue has attracted the attention of researchers in the anti-obesity field. Although MetAP2 inhibitors were originally developed as anti-cancer therapies, as described above, MetAP2 inhibitors target angiogenesis, which would prevent further development of adipose tissue and thus obesity. Unlike anti-angiogenic therapy for cancer, MetAP2 inhibition for obesity treatment might not lead to drug resistance due to the genomic stability of obesity-related adipocytes and endothelial cells[62]. In addition, the timescale of current obesity treatment are not designed for longitudinal study and the treatment can be stopped when target body weight is achieved[62]. Since angiogenesis is important for wound healing, it is predicted that patients who are obese and have already developed cardiometabolic complications, such as hypertension, might not be appropriate for this type of therapy[63].

ZGN-433 (beloranib, CKD-732) described above, was found to be an effective MetAP-2 inhibitor for anti-diabetes. In the phase II study, beloranib produced statistically significant and clinically meaningful weight loss in obese participants for up to 12 wk in the absence of any dietary or exercise intervention[63]. Statistically significant improvements in cardiometabolic risk factors, including waist circumference, lipids and blood pressure, were observed when compared to a placebo. Overall, adverse events were mild to moderate, and they are resolved over the course of the study. Robust Phase II clinical data of ZGN-433 (beloranib) indicated that a high potential for weight reduction in moderate to severe obese patients without serious adverse effects. Beloranib has moved into Phase III clinical trials[64]. Unfortunately, in December 2015, there was a second patient death. In order to determine whether the deaths were treatment related, Zafgen halted the Phase III clinical trial of beloranib for Prader-Willi Syndrome. After discussions with the Food and Drug Administration, they found that there are insurmountable obstacles to gaining approval and thus, product development for beloranib was ended.

**REVERSIBLE *VS* IRREVERSIBLE METHIONINE AMINOPEPTIDASE INHIBITORS**

All the MetAP2 inhibitors that have entered clinical trials so far are irreversible inhibitors containing a highly reactive spiroepoxide (Table 1). It remains unclear whether the major adverse effects are caused by the interaction of the spiroepoxide with non-specific targets or simply the nature of the biological function of eMetAP2. Many reversible MetAP2 inhibitors have been developed (Table 1). They include bengamides, 2-hydroxy-3-aminoamides, anthranilic acid sulfonamides and triazole analogs[65-68]. Most of the reversible MetAP2 inhibitors, except the bengamides, have not entered clinical trials because they are not as potent as irreversible[66]. Recently, using the fragment-based drug discovery approach (FBDD), a 6-substituted indazole core was identified as anorally efficacious potent reversible MetAP2 inhibitor[69]. Based on those findings, a pyrozolo[4,3-b]indole core was designed using the structure-based drug discovery (SBDD) approach[70]. One pharmacokinetically acceptable compoundwas further evaluated in a DIO-mouse model for obesity and a 4% reduction in body weight was observedl. In addition, this compound was high specific based on the data evaluated in a Ricerca Comprehensive Pharmacological Profile panel including 100 biological targets and a panel of proteases[69,70]. These findings showed great promise of developing potent reversible MetAP2 inhibitors for obesity and hopefully for anti-cancer drugs in the foreseeable future.

**CONCLUSION**

Despite initial promising pre-clinical and clinical studies using MetAP2 as the target for anti-cancer and anti-obesity drug development, many important biological questions remain unsolved. Insights into the basic biology of eMetAPs have only recently emerged. These include a recent large-scale N-terminus profiling in cells responsive and unresponsive to fumagillin treatment[71]. Changes in glutathione status were observed in fumagillin-sensitive cells, but not in unresponsive cells. Proteo-transcriptomic analyses revealed that both eMetAPs accumulated in a cell-specific manner and that cell sensitivity to fumagillin was related to the expression levels of eMetAPs, particularly eMetAP1. It is also worth noting that the authors suggested that MetAP1 levels could be routinely checked in several types of tumors and used as a prognostic marker for predicting responses to treatments inhibiting MetAP2[71]. Moreover, additional publications have allowed a growing understanding of the regulation of the MetAPs and the interplay between MetAPs, ribosomes, and other factors involved in protein synthesis and protein processing, as well as the regulation of MetAP functions[72-74]. These significant advances in our understandings of these basic biological functions will help advance the development of potent anti-cancer and anti-obesity MetAP inhibitors to significantly reduce the risk of unexpected adverse effects occur during clinical trials.

**REFERENCES**

1 **Maksimov ML**, Svistunov AA, Tarasov VV, Chubarev VN, Ávila-Rodriguez M, Barreto GE, Dralova OV, Aliev G. Approaches for the Development of Drugs for Treatment of Obesity and Metabolic Syndrome. *Curr Pharm Des* 2016; **22**: 895-903 [PMID: 26648466 DOI: 10.2174/1381612822666151209153047]

2 **Korner J**, Aronne LJ. The emerging science of body weight regulation and its impact on obesity treatment. *J Clin Invest* 2003; **111**: 565-570 [PMID: 12618507 DOI: 10.1172/JCI200317953]

3 **Friedman JM**. Obesity in the new millennium. *Nature* 2000; **404**: 632-634 [PMID: 10766249]

4 **Kopelman PG**. Obesity as a medical problem. *Nature* 2000; **404**: 635-643 [PMID: 10766250]

5 **Cao Y**. Angiogenesis modulates adipogenesis and obesity. *J Clin Invest* 2007; **117**: 2362-2368 [PMID: 17786229 DOI: 10.1172/JCI32239]

6 **Lupo G**, Caporarello N, Olivieri M, Cristaldi M, Motta C, Bramanti V, Avola R, Salmeri M, Nicoletti F, Anfuso CD. Anti-angiogenic Therapy in Cancer: Downsides and New Pivots for Precision Medicine. *Front Pharmacol* 2016; **7**: 519 [PMID: 28111549 DOI: 10.3389/fphar.2016.00519]

7 **Sin N**, Meng L, Wang MQ, Wen JJ, Bornmann WG, Crews CM. The anti-angiogenic agent fumagillin covalently binds and inhibits the methionine aminopeptidase, MetAP-2. *Proc Natl Acad Sci USA* 1997; **94**: 6099-6103 [PMID: 9177176 DOI: 10.1073/pnas.94.12.6099]

8 **Griffith EC**, Su Z, Turk BE, Chen S, Chang YH, Wu Z, Biemann K, Liu JO. Methionine aminopeptidase (type 2) is the common target for angiogenesis inhibitors AGM-1470 and ovalicin. *Chem Biol* 1997; **4**: 461-471 [PMID: 9224570 DOI: 10.1016/s1074-5521(97)90198-8]

9 **Turk BE**, Su Z, Liu JO. Synthetic analogues of TNP-470 and ovalicin reveal a common molecular basis for inhibition of angiogenesis and immunosuppression. *Bioorg Med Chem* 1998; **6**: 1163-1169 [PMID: 9784858 DOI: 10.1016/s0968-0896(98)00078-9]

10 **Liu S**, Widom J, Kemp CW, Crews CM, Clardy J. Structure of human methionine aminopeptidase-2 complexed with fumagillin. *Science* 1998; **282**: 1324-1327 [PMID: 9812898 DOI: 10.1126/science.282.5392.1324]

11 **Nonato MC**, Widom J, Clardy J. Human methionine aminopeptidase type 2 in complex with L- and D-methionine. *Bioorg Med Chem Lett* 2006; **16**: 2580-2583 [PMID: 16540317 DOI: 10.1016/j.bmcl.2006.02.047]

12 **Turk BE**, Griffith EC, Wolf S, Biemann K, Chang YH, Liu JO. Selective inhibition of amino-terminal methionine processing by TNP-470 and ovalicin in endothelial cells. *Chem Biol* 1999; **6**: 823-833 [PMID: 10574784 DOI: 10.1016/s1074-5521(99)80129-x]

13 **Zhang Y**, Griffith EC, Sage J, Jacks T, Liu JO. Cell cycle inhibition by the anti-angiogenic agent TNP-470 is mediated by p53 and p21WAF1/CIP1. *Proc Natl Acad Sci USA* 2000; **97**: 6427-6432 [PMID: 10841547 DOI: 10.1073/pnas.97.12.6427]

14 **Tsunasawa S**, Stewart JW, Sherman F. Amino-terminal processing of mutant forms of yeast iso-1-cytochrome c. The specificities of methionine aminopeptidase and acetyltransferase. *J Biol Chem* 1985; **260**: 5382-5391 [PMID: 2985590 DOI: 10.1002/0470028637.met025]

15 **Huang S**, Elliott RC, Liu PS, Koduri RK, Weickmann JL, Lee JH, Blair LC, Ghosh-Dastidar P, Bradshaw RA, Bryan KM. Specificity of cotranslational amino-terminal processing of proteins in yeast. *Biochemistry* 1987; **26**: 8242-8246 [PMID: 3327521 DOI: 10.1021/bi00399a033]

16 **Moerschell RP**, Hosokawa Y, Tsunasawa S, Sherman F. The specificities of yeast methionine aminopeptidase and acetylation of amino-terminal methionine in vivo. Processing of altered iso-1-cytochromes c created by oligonucleotide transformation. *J Biol Chem* 1990; **265**: 19638-19643 [PMID: 2174047]

17 **Ben-Bassat A**, Bauer K, Chang SY, Myambo K, Boosman A, Chang S. Processing of the initiation methionine from proteins: properties of the Escherichia coli methionine aminopeptidase and its gene structure. *J Bacteriol* 1987; **169**: 751-757 [PMID: 3027045 DOI: 10.1128/jb.169.2.751-757.1987]

18 **Miller CG**, Strauch KL, Kukral AM, Miller JL, Wingfield PT, Mazzei GJ, Werlen RC, Graber P, Movva NR. N-terminal methionine-specific peptidase in Salmonella typhimurium. *Proc Natl Acad Sci USA* 1987; **84**: 2718-2722 [PMID: 3106976 DOI: 10.1073/pnas.84.9.2718]

19 **Hirel PH**, Schmitter MJ, Dessen P, Fayat G, Blanquet S. Extent of N-terminal methionine excision from Escherichia coli proteins is governed by the side-chain length of the penultimate amino acid. *Proc Natl Acad Sci USA* 1989; **86**: 8247-8251 [PMID: 2682640 DOI: 10.1073/pnas.86.21.8247]

20 **Chang SY**, McGary EC, Chang S. Methionine aminopeptidase gene of Escherichia coli is essential for cell growth. *J Bacteriol* 1989; **171**: 4071-4072 [PMID: 2544569 DOI: 10.1128/jb.171.7.4071-4072.1989]

21 **Chang YH**, Teichert U, Smith JA. Purification and characterization of a methionine aminopeptidase from Saccharomyces cerevisiae. *J Biol Chem* 1990; **265**: 19892-19897 [PMID: 2246265]

22 **Kendall RL**, Bradshaw RA. Isolation and characterization of the methionine aminopeptidase from porcine liver responsible for the co-translational processing of proteins. *J Biol Chem* 1992; **267**: 20667-20673 [PMID: 1328207]

23 **Chang YH**, Teichert U, Smith JA. Molecular cloning, sequencing, deletion, and overexpression of a methionine aminopeptidase gene from Saccharomyces cerevisiae. *J Biol Chem* 1992; **267**: 8007-8011 [PMID: 1569059]

24 **Li X**, Chang YH. Molecular cloning of a human complementary DNA encoding an initiation factor 2-associated protein (p67). *Biochim Biophys Acta* 1995; **1260**: 333-336 [PMID: 7873610 DOI: 10.1016/0167-4781(94)00227-t]

25 **Li X**, Chang YH. Amino-terminal protein processing in Saccharomyces cerevisiae is an essential function that requires two distinct methionine aminopeptidases. *Proc Natl Acad Sci USA* 1995; **92**: 12357-12361 [PMID: 8618900 DOI: 10.1073/pnas.92.26.12357]

26 **Arfin SM**, Kendall RL, Hall L, Weaver LH, Stewart AE, Matthews BW, Bradshaw RA. Eukaryotic methionyl aminopeptidases: two classes of cobalt-dependent enzymes. *Proc Natl Acad Sci USA* 1995; **92**: 7714-7718 [PMID: 7644482 DOI: 10.1073/pnas.92.17.7714]

27 **Lowther WT**, Matthews BW. Metalloaminopeptidases: common functional themes in disparate structural surroundings. *Chem Rev* 2002; **102**: 4581-4608 [PMID: 12475202 DOI: 10.1021/cr0101757]

28 **Zuo S**, Guo Q, Chang YH. A protease assay via precolumn derivatization and high-performance liquid chromatography. *Anal Biochem* 1994; **222**: 514-516 [PMID: 7864384 DOI: 10.1006/abio.1994.1529]

29 **Zuo S**, Guo Q, Ling C, Chang YH. Evidence that two zinc fingers in the methionine aminopeptidase from Saccharomyces cerevisiae are important for normal growth. *Mol Gen Genet* 1995; **246**: 247-253 [PMID: 7862096 DOI: 10.1007/bf00294688]

30 **Vetro JA**, Chang YH. Yeast methionine aminopeptidase type 1 is ribosome-associated and requires its N-terminal zinc finger domain for normal function in vivo. *J Cell Biochem* 2002; **85**: 678-688 [PMID: 11968008 DOI: 10.1002/jcb.10161]

31 **Vetro JA**, Dummitt B, Micka WS, Chang YH. Evidence of a dominant negative mutant of yeast methionine aminopeptidase type 2 in Saccharomyces cerevisiae. *J Cell Biochem* 2005; **94**: 656-668 [PMID: 15547949 DOI: 10.1002/jcb.20285]

32 **Nyathi Y**, Pool MR. Analysis of the interplay of protein biogenesis factors at the ribosome exit site reveals new role for NAC. *J Cell Biol* 2015; **210**: 287-301 [PMID: 26195668 DOI: 10.1083/jcb.201410086]

33 **Datta B**. MAPs and POEP of the roads from prokaryotic to eukaryotic kingdoms. *Biochimie* 2000; **82**: 95-107 [PMID: 10727764 DOI: 10.1016/s0300-9084(00)00383-7]

34 **Chen S**, Vetro JA, Chang YH. The specificity in vivo of two distinct methionine aminopeptidases in Saccharomyces cerevisiae. *Arch Biochem Biophys* 2002; **398**: 87-93 [PMID: 11811952 DOI: 10.1006/abbi.2001.2675]

35 **Giglione C**, Vallon O, Meinnel T. Control of protein life-span by N-terminal methionine excision. *EMBO J* 2003; **22**: 13-23 [PMID: 12505980 DOI: 10.1093/emboj/cdg007]

36 **Dummitt B**, Micka WS, Chang YH. Yeast glutamine-fructose-6-phosphate aminotransferase (Gfa1) requires methionine aminopeptidase activity for proper function. *J Biol Chem* 2005; **280**: 14356-14360 [PMID: 15699032 DOI: 10.1074/jbc.m501059200]

37 **Folkman J**. Tumor angiogenesis. *Adv Cancer Res* 1985; **43**: 175-203 [PMID: 2581424 DOI: 10.1016/s0065-230x(08)60946-x]

38 **Folkman J**. Angiogenesis in cancer, vascular, rheumatoid and other disease. *Nat Med* 1995; **1**: 27-31 [PMID: 7584949 DOI: 10.1038/nm0195-27]

39 **Risau W**. Mechanisms of angiogenesis. *Nature* 1997; **386**: 671-674 [PMID: 9109485 DOI: 10.1038/386671a0]

40 **Gimbrone MA**, Leapman SB, Cotran RS, Folkman J. Tumor dormancy in vivo by prevention of neovascularization. *J Exp Med* 1972; **136**: 261-276 [PMID: 5043412 DOI: 10.1084/jem.136.2.261]

41 **Hanahan D**, Folkman J. Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis. *Cell* 1996; **86**: 353-364 [PMID: 8756718 DOI: 10.1016/s0092-8674(00)80108-7]

42 **Ingber D**, Fujita T, Kishimoto S, Sudo K, Kanamaru T, Brem H, Folkman J. Synthetic analogues of fumagillin that inhibit angiogenesis and suppress tumour growth. *Nature* 1990; **348**: 555-557 [PMID: 1701033 DOI: 10.1038/348555a0]

43 **Folkman J**. Seminars in Medicine of the Beth Israel Hospital, Boston. Clinical applications of research on angiogenesis. *N Engl J Med* 1995; **333**: 1757-1763 [PMID: 7491141]

44 **Folkman J**. Tumor angiogenesis: therapeutic implications. *N Engl J Med* 1971; **285**: 1182-1186 [PMID: 4938153 DOI: 10.1056/NEJM197111182852108]

45 **Kusaka M**, Sudo K, Fujita T, Marui S, Itoh F, Ingber D, Folkman J. Potent anti-angiogenic action of AGM-1470: comparison to the fumagillin parent. *Biochem Biophys Res Commun* 1991; **174**: 1070-1076 [PMID: 1705118 DOI: 10.1016/0006-291x(91)91529-l]

46 **Eble TE**, Hanson FR. Fumagillin, an antibiotic from Aspergillus funigatus H-3. *Antibiot Chemother* (Northfield) 1951; **1**: 54-58 [PMID: 24540610]

47 **Marui S**, Itoh F, Kozai Y, Sudo K, Kishimoto S. Chemical modification of fumagillin. I. 6-O-acyl, 6-O-sulfonyl, 6-O-alkyl, and 6-O-(N-substituted-carbamoyl)fumagillols. *Chem Pharm Bull* (Tokyo) 1992; **40**: 96-101 [PMID: 1374294 DOI: 10.1248/cpb.40.96]

48 **Folkman J**. Tumor angiogenesis. In: Wells SA Jr, Sharp PA: Accomplishments in Cancer Research. Pennsylvania: JB Lippincott Williams and Wilkins, 1998: 32-44

49 **Bernier SG**, Lazarus DD, Clark E, Doyle B, Labenski MT, Thompson CD, Westlin WF, Hannig G. A methionine aminopeptidase-2 inhibitor, PPI-2458, for the treatment of rheumatoid arthritis. *Proc Natl Acad Sci USA* 2004; **101**: 10768-10773 [PMID: 15249666 DOI: 10.1073/pnas.0404105101]

50 **Lefkove B**, Govindarajan B, Arbiser JL. Fumagillin: an anti-infective as a parent molecule for novel angiogenesis inhibitors. *Expert Rev Anti Infect Ther* 2007; **5**: 573-579 [PMID: 17678422 DOI: 10.1586/14787210.5.4.573]

51 **Antoine N**, Greimers R, De Roanne C, Kusaka M, Heinen E, Simar LJ, Castronovo V. AGM-1470, a potent angiogenesis inhibitor, prevents the entry of normal but not transformed endothelial cells into the G1 phase of the cell cycle. *Cancer Res* 1994; **54**: 2073-2076 [PMID: 7513609]

52 **Olson GL**, Self C, Lee L, Cook CM, Birktoft JJ. Therapeutic agents and methods of use thereof for the modulation of angiogenesis. United States patent US 6548477. Praecis Pharmaceuticals Inc., 2003 Apr 15

53 **Arico-Muendel CC**, Benjamin DR, Caiazzo TM, Centrella PA, Contonio BD, Cook CM, Doyle EG, Hannig G, Labenski MT, Searle LL, Lind K, Morgan BA, Olson G, Paradise CL, Self C, Skinner SR, Sluboski B, Svendsen JL, Thompson CD, Westlin W, White KF. Carbamate analogues of fumagillin as potent, targeted inhibitors of methionine aminopeptidase-2. *J Med Chem* 2009; **52**: 8047-8056 [PMID: 19929003 DOI: 10.1021/jm901260k]

54 **Hannig G**, Lazarus DD, Bernier SG, Karp RM, Lorusso J, Qiu D, Labenski MT, Wakefield JD, Thompson CD, Westlin WF. Inhibition of melanoma tumor growth by a pharmacological inhibitor of MetAP-2, PPI-2458. *Int J Oncol* 2006; **28**: 955-963 [PMID: 16525646 DOI: 10.3892/ijo.28.4.955]

55 **Cooper AC**, Karp RM, Clark EJ, Taghizadeh NR, Hoyt JG, Labenski MT, Murray MJ, Hannig G, Westlin WF, Thompson CD. A novel methionine aminopeptidase-2 inhibitor, PPI-2458, inhibits non-Hodgkin's lymphoma cell proliferation in vitro and in vivo. *Clin Cancer Res* 2006; **12**: 2583-2590 [PMID: 16638869 DOI: 10.1158/1078-0432.CCR-05-0871]

56 **Hannig G**, Bernier SG, Hoyt JG, Doyle B, Clark E, Karp RM, Lorusso J, Westlin WF. Suppression of inflammation and structural damage in experimental arthritis through molecular targeted therapy with PPI-2458. *Arthritis Rheum* 2007; **56**: 850-860 [PMID: 17328059 DOI: 10.1002/art.22402]

57 **Bainbridge J**, Madden L, Essex D, Binks M, Malhotra R, Paleolog EM. Methionine aminopeptidase-2 blockade reduces chronic collagen-induced arthritis: potential role for angiogenesis inhibition. *Arthritis Res Ther* 2007; **9**: R127 [PMID: 18072970 DOI: 10.1186/ar2340]

58 **Ashraf S**, Mapp PI, Walsh DA. Angiogenesis and the persistence of inflammation in a rat model of proliferative synovitis. *Arthritis Rheum* 2010; **62**: 1890-1898 [PMID: 20309868 DOI: 10.1002/art.27462]

59 **Satchi-Fainaro R**, Mamluk R, Wang L, Short SM, Nagy JA, Feng D, Dvorak AM, Dvorak HF, Puder M, Mukhopadhyay D, Folkman J. Inhibition of vessel permeability by TNP-470 and its polymer conjugate, caplostatin. *Cancer Cell* 2005; **7**: 251-261 [PMID: 15766663 DOI: 10.1016/j.ccr.2005.02.007]

60 **Stadler WM**, Kuzel T, Shapiro C, Sosman J, Clark J, Vogelzang NJ. Multi-institutional study of the angiogenesis inhibitor TNP-470 in metastatic renal carcinoma. *J Clin Oncol* 1999; **17**: 2541-2545 [PMID: 10561320 DOI: 10.1200/jco.1999.17.8.2541]

61 **Shin SJ**, Ahn JB, Park KS, Lee YJ, Hong YS, Kim TW, Kim HR, Rha SY, Roh JK, Kim DH, Kim C, Chung HC. A Phase Ib pharmacokinetic study of the anti-angiogenic agent CKD-732 used in combination with capecitabine and oxaliplatin (XELOX) in metastatic colorectal cancer patients who progressed on irinotecan-based chemotherapy. *Invest New Drugs* 2012; **30**: 672-680 [PMID: 21188464 DOI: 10.1007/s10637-010-9625-x]

62 **Cao Y**. Adipose tissue angiogenesis as a therapeutic target for obesity and metabolic diseases. *Nat Rev Drug Discov* 2010; **9**: 107-115 [PMID: 20118961 DOI: 10.1038/nrd3055]

63 **Joharapurkar AA**, Dhanesha NA, Jain MR. Inhibition of the methionine aminopeptidase 2 enzyme for the treatment of obesity. *Diabetes Metab Syndr Obes* 2014; **7**: 73-84 [PMID: 24611021 DOI: 10.2147/DMSO.S56924]

64 **ClinicalTrials.gov**. [Accessed 2015 Aug 24]. Available from: URL: http://clinicaltrials.gov

65 **Martín-Gálvez F**, García-Ruiz C, Sánchez-Ruiz A, Valeriote FA, Sarabia F. An array of bengamide E analogues modified at the terminal olefinic position: synthesis and antitumor properties. *ChemMedChem* 2013; **8**: 819-831 [PMID: 23512621 DOI: 10.1002/cmdc.201300033]

66 **Yin SQ**, Wang JJ, Zhang CM, Liu ZP. The development of MetAP-2 inhibitors in cancer treatment. *Curr Med Chem* 2012; **19**: 1021-1035 [PMID: 22229417]

67 **Wang J**, Tucker LA, Stavropoulos J, Zhang Q, Wang YC, Bukofzer G, Niquette A, Meulbroek JA, Barnes DM, Shen J, Bouska J, Donawho C, Sheppard GS, Bell RL. Correlation of tumor growth suppression and methionine aminopetidase-2 activity blockade using an orally active inhibitor. *Proc Natl Acad Sci USA* 2008; **105**: 1838-1843 [PMID: 18252827 DOI: 10.1073/pnas.0708766105]

68 **Marino JP**, Fisher PW, Hofmann GA, Kirkpatrick RB, Janson CA, Johnson RK, Ma C, Mattern M, Meek TD, Ryan MD, Schulz C, Smith WW, Tew DG, Tomazek TA, Veber DF, Xiong WC, Yamamoto Y, Yamashita K, Yang G, Thompson SK. Highly potent inhibitors of methionine aminopeptidase-2 based on a 1,2,4-triazole pharmacophore. *J Med Chem* 2007; **50**: 3777-3785 [PMID: 17636946]

69 **Cheruvallath Z**, Tang M, McBride C, Komandla M, Miura J, Ton-Nu T, Erikson P, Feng J, Farrell P, Lawson JD, Vanderpool D, Wu Y, Dougan DR, Plonowski A, Holub C, Larson C. Discovery of potent, reversible MetAP2 inhibitors via fragment based drug discovery and structure based drug design-Part 1. *Bioorg Med Chem Lett* 2016; **26**: 2774-2778 [PMID: 27155900 DOI: 10.1016/j.bmcl.2016.04.073]

70 **McBride C**, Cheruvallath Z, Komandla M, Tang M, Farrell P, Lawson JD, Vanderpool D, Wu Y, Dougan DR, Plonowski A, Holub C, Larson C. Discovery of potent, reversible MetAP2 inhibitors via fragment based drug discovery and structure based drug design-Part 2. *Bioorg Med Chem Lett* 2016; **26**: 2779-2783 [PMID: 27136719 DOI: 10.1016/j.bmcl.2016.04.072]

71 **Frottin F**, Bienvenut WV, Bignon J, Jacquet E, Vaca Jacome AS, Van Dorsselaer A, Cianferani S, Carapito C, Meinnel T, Giglione C. MetAP1 and MetAP2 drive cell selectivity for a potent anti-cancer agent in synergy, by controlling glutathione redox state. *Oncotarget* 2016; **7**: 63306-63323 [PMID: 27542228 DOI: 10.18632/oncotarget.11216]

72 **Ng JY**, Chiu J, Hogg PJ, Wong JW. Tyrosine nitration moderates the peptidase activity of human methionyl aminopeptidase 2. *Biochem Biophys Res Commun* 2013; **440**: 37-42 [PMID: 24041691 DOI: 10.1016/j.bbrc.2013.09.035]

73 **Bornemann T**, Holtkamp W, Wintermeyer W. Interplay between trigger factor and other protein biogenesis factors on the ribosome. *Nat Commun* 2014; **5**: 4180 [PMID: 24939037 DOI: 10.1038/ncomms5180]

74 **Giglione C**, Fieulaine S, Meinnel T. N-terminal protein modifications: Bringing back into play the ribosome. *Biochimie* 2015; **114**: 134-146 [PMID: 25450248 DOI: 10.1016/j.biochi.2014.11.008]

**P-Reviewer:** Chen YC, Guo Q, He S, Wang L **S-Editor:** Ji FF **L-Editor: E-Editor:**

**Table 1 Current status of selected MetAP2 inhibitors**

|  |
| --- |
| Name type of inhibitor preclinical/clinical trails |
| Fumagillin[7-10]  | Irreversible | N/A |
| TNP-470[12,13]  | Irreversible | Phase I |
| PPI-2458[49]  | Irreversible | Phase I |
| CKD-732[61-64] (ZGN-433, beloranib) | Irreversible | Phase II/III |
| SDX-7320[59,60] | Irreversible | Phase II |
| Bengamides[65] (LAF389) | Reversible | Phase I |
| 2-Hydroxy-3-aminoamides[66] | Reversible | Preclinical |
| Anthranilic acid sulfonamides[67]  | Reversible | Preclinical |
| Triazoles[68] | Reversible | Preclinical |
| Indazoles[69]  | Reversible | Preclinical |
| Pyrozolo[4,3-b]indoles[70]  | Reversible | Preclinical |