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EDITORIAL

Common therapeutic target for both cancer and obesity

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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 amino-peptidase (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

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.

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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 (MetAPs) to both cancer and obesity.

TWO DISTINCT TYPES OF EUKARYOTIC METAPS ARE RIBOSOME-ASSOCIATED METALLOPROTEASES AND EMETAP2 IS BI-FUNCTIONAL

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 MetAPs 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.

METAPS 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

Table 1 Current status of selected type-2 methionine aminopeptidase 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
Pyrazolo[4,3-b]indoles[70]	Reversible	Preclinical

N/A: Not applicable.

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 an orally efficacious potent reversible MetAP2 inhibitor[69]. Based on those findings, a pyrazolo[4,3-b]indole core was designed using the structure-based drug discovery (SBDD) approach[70]. One pharmacokinetically acceptable compound was further evaluated in a DIO-mouse model for obesity and a 4% reduction in body weight was observed. 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.

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