

N-Terminal Methionine Excision

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In the cytosol of human cells, when a newly synthesized polypeptide emerges from the ribosomes, its fate can be determined by the enzymes that modify its N-terminal α -amino acid residue (N^α). These N-terminal modifications include excision of the initiator methionine (iMet), N^α -myristoylation, N^α -acetylation, N^α -methylation, and other less common modification events. Methionine aminopeptidases (MetAPs) are responsible for N-terminal iMet excision (NME).

methionine aminopeptidases

N-terminal iMet excision

1. Introduction

In the cytosol of human cells, when a newly synthesized polypeptide emerges from the ribosomes, its fate can be determined by the enzymes that modify its N-terminal α -amino acid residue (N^α). These N-terminal modifications include excision of the initiator methionine (iMet), N^α -myristoylation, N^α -acetylation, N^α -methylation, and other less common modification events such as N^α -propionylation, N^α -palmitoylation, N^α -arginylation, and N^α -ubiquitylation. Among these enzymes, methionine aminopeptidases (MetAPs) are responsible for N-terminal iMet excision (NME) [1][2]; N-terminal acetyltransferases (NATs) for N^α -acetylation [3]; N-terminal myristoyltransferase (NMTs) for N^α -myristoylation [4]; N-terminal methylation for N^α -methylation (NTMTs) [5]; N-terminal palmitoylacyltransferases (PATs) for N^α -palmitoylation [6]; and ubiquitin ligases for ubiquitylation of the N-terminal α -amino acid residue [7]. The NATs can also sometimes catalyze a much less understood modification: N^α -propionylation [8]. These modifications of proteins at their N-termini play critical roles in many important cellular processes, and dysregulation of these events could significantly impact the development and progression of certain human diseases [9][10].

2. N-Terminal Methionine Excision (NME)

Protein synthesis in the cytosol of a eukaryotic cell, in most cases, is initiated with methionine. When the second amino acid residue is a small and uncharged amino acid such as Ala, Cys, Gly, Pro, Ser, Thr, or Val, iMet is usually removed co-translationally by two types of methionine aminopeptidases (MetAPs) [11][12][13][14][15][16][17][18][19][20]. Although these two types do not share a high sequence identity, their catalytic domains belong to the same family of metalloproteases with a typical "pita-bread" protease fold [19]. The N-terminal domain of eukaryotic MetAP1s contains two zinc finger motifs; a RING-finger-like Cys2-Cys2 zinc finger and a Cys2-His2 zinc finger related to RNA-binding zinc fingers [21][22]. These two zinc fingers are essential for the regular functional association of MetAP1 with the ribosomes [21][22]. On the other hand, eukaryotic type 2 MetAPs (MetAP2s) contain an N-terminal

domain with a positively charged Lys-rich region [16][17][18][19][20]. Deleting MetAP1 in yeast leads to a slow growth phenotype which can be rescued by overexpressing MetAP2, whereas knocking out both MetAPs is lethal, indicating that the NME process is vital for normal cell growth (Table 1) [17]. This finding strongly suggests that both enzymes act on similar groups of substrates in vivo. Structural studies of human MetAPs revealed a potential difference in the substrate specificity of their catalytic sites due to more steric restrictions in MetAP1 [20]. Proteomics analysis of the substrate specificity of human MetAPs indicates that MetAP2 prefers iMet-Val and iMet-Thr. However, substrate specificity significantly overlaps between human MetAP1 and MetAP2 [15].

Table 1. Impact of protein N^α-modifications on cellular functions.

Enzymes	Cellular Functions	References
MetAP1	Cell cycle progression, cell proliferation, enzyme function, protein stability, cellular localization	[13][14][15][16][17][18] [19][20][21][22][23]
MetAP2	Angiogenesis, B-cell differentiation, cell-specific Cytotoxicity	[23][24][25][26][27][28] [29][30][31][32][33][34]
NMTs	Signal transduction, cellular transformation, innate immune responses, adaptative immune response	[35][36][37][38]
NATs	Actin cytoskeleton structure, cell cycle progression, cell proliferation cell mobility	[39][40][41][42][43][44] [45][46][47][48]
NTMTs	Protein stability, protein-protein interaction, protein-DNA interaction, cellular localization, response to cellular stress, DNA repair, regulation of mitosis, chromatin interaction, tRNA transport, genome stability	[5][49][50][51][52][53] [54][55][56][57][58]

Since discovering that human MetAP2, not human MetAP1, is the molecular target of TNP-470, a potent anti-angiogenesis inhibitor, MetAP2 has become a drug target for treating cancer, obesity, Prader-Willi Syndrome (PWS), and autoimmunity (Table 2) [23][24][25][26]. Inhibitors for human MetAP2 are well tolerated in patients at therapeutically relevant doses and have been developed for a variety of pharmaceutical applications, including the treatment of cancer [27][28][29][30][31], diabetes, and obesity [32], as well as the modulation of autoimmunity [33][34]. Although none of these inhibitors have yet passed Phase III clinical trials, the interest of the drug development community remains high due to continued promising preclinical and clinical efficacy results for novel MetAP2 inhibitors. Unfortunately, most studies did not assess the impact of MetAP2 inhibition on cellular functions, making it harder to correlate the phenotypes to the inhibitors' mode of action. Most of the time, more questions were raised than answered regarding the role of MetAP2 in these diseases after a new clinical study. For example, it is still being determined whether the molecular mechanisms driving each phenotype discovered during each clinical trial share the exact molecular mechanisms. The molecular mechanisms of MetAP2 inhibitor-induced weight loss or immune modulation remain to be established. Even the fundamental questions regarding the substrate specificity of MetAPs in different tissues still need to be better defined. Indeed, a better understanding of MetAP biology and the mode of action of MetAP2 inhibitors would undoubtedly improve the quality of biomarkers for patient screening, the identification of novel indications, and the development of evidence-based drug combinations in targeted disease treatment.

Table 2. Potential targets for developing a novel treatment for human diseases.

Enzymes	Targeted Human Diseases	References
MetAP1	Antibiotics, cancer	[20]
MetAP1D	Colon cancer	[59][60]
MetAP2	Cancer, obesity, diabetes, Prader-Willi syndrome, autoimmunity	[23][24][25][26][27][28][29][30][31][32][33] [34]
NMTs	Cancer; HIV, fungal, and parasitic infection	[61][62][63][64][65][66][67][68][69][70]
NATs	Cancer (lung, liver, colon), Parkinson's disease	[71][72][73][74][75][76][77][78][79][80][81]
NTMTs	Cancer (breast, colon, pancreatic, lung)	[82][83][84][85][86][87][88][89]

In the mitochondria of human cells, protein synthesis is initiated with formyl-methionine. A deformylase can remove the formyl group to expose an unmodified methionine, which becomes a substrate for MetAP. A search of the GenBank database with cytosolic MetAP1 and MetAP2 protein sequences led to the discovery of MetAP1D [59]. MetAP1D is a new member of the human MetAP family and belongs to the Type I MetAP subfamily. Phylogenetic analysis of human MetAP isoforms suggests that human MetAP1D pairs with mitochondrial MetAP orthologs previously identified in plants [90]. All three MetAP isoforms can remove Met from a Met-Ala-Ser peptide in vitro. However, the substrate specificity of MetAP1D has not been thoroughly investigated. MetAP1D is overexpressed in colon cancer cells and colon tumors. Reduced expression of MetAP1D by shRNA has been shown to decrease the ability of colon cancer cells to grow in soft agar, indicating that overexpression of MetAP1D may be necessary for tumorigenesis. Thus, MAP1D has been suggested to be a target for chemotherapy in colon carcinoma [59][60].

Recently, genomic analyses demonstrated that patients with intellectual disability (ID) harbor a novel homozygous nonsense mutation in the *MetAP1* gene. ID is a common genetic and clinically heterogeneous disease, and underlying molecular pathogenesis can frequently be unidentified by whole-exome/genome testing. Improper neuronal function from losing essential proteins could lead to neurologic impairment and ID [91]. In addition, a mutation in the *MetAP1D* gene was identified as one candidate involved in the penetrance of Leber’s hereditary optic neuropathy (LHON) [92]. Though researchers are still very early in understanding how mutations in MetAPs could affect human health, NME excision processes provide a promising avenue in translational research.

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