The amyloid peptide is the main constituent of the amyloid plaques in brain of Alzheimer’s disease patients. This peptide is generated from the amyloid precursor protein by two consecutive cleavages. Cleavage at the N terminus is performed by the recently discovered \( \beta \)-secretase (Bace). This aspartyl protease contains a propeptide that has to be removed to obtain mature Bace. Furin and other members of the furin family of prohormone convertases are involved in this process. Surprisingly, \( \beta \)-secretase activity, neither at the classical Asp\(^1 \) position nor at the Glu\(^{11} \) position of amyloid precursor protein, seems to be controlled by this maturation step. Furthermore, we show that Glu\(^{11} \) cleavage is a function of the expression level of Bace, that it depends on the membrane anchorage of Bace, and that Asp\(^{1} \) cleavage can be followed by Glu\(^{11} \) cleavage. Our data suggest that pro-Bace could be active as a \( \beta \)-secretase in the early biosynthetic compartments of the cell and could be involved in the generation of the intracellular pool of the amyloid peptide. We conclude that modulation of the conversion of pro-Bace to mature Bace is not a relevant drug target to treat Alzheimer’s disease.

The brain of patients suffering from Alzheimer’s disease (AD)\(^{1} \) is characterized by the presence of amyloid plaques composed mainly of the 39–42 amino acid amyloid \( \beta \)(A\(\beta \)) peptide (1, 2). A\(\beta \) derives from a type I single membrane-spanning protein termed amyloid precursor protein (APP) by post-translational proteolytic cleavage (3). Two cleavages by \( \beta \)-and \( \gamma \)-secretases, respectively, are required to release A\(\beta \) from APP.

Only recently the molecular identity of these enzymes has been elucidated. \( \gamma \)-Secretase is apparently a large complex, with presenilin being an essential component of it (4–7). \( \beta \)-Secretase has been identified independently by 5 groups and was named Bace (\( \beta \)-site APP cleaving enzyme, A\(\beta \)-2, or memapsin 2 (membrane-anchored aspartic peptide of the pepsin family) (8–12). Bace is a type I integral membrane protein, with a typical aspartyl protease motif in its luminal domain. Bace fulfills most of the requirements expected for a candidate \( \beta \)-secretase. It has broad tissue distribution with higher expression in the brain (8–10). It localizes mainly in Golgi and endosomes (8, 9). Bace overexpression increases, and treatment of cells with antisense oligonucleotides complementary to Bace mRNA decreases \( \beta \)-secretase cleavage of APP (8–12). Bace is a transmembrane protein whose predicted topology is correct with respect to the \( \beta \)-secretase cleavage site in APP. It cleaves more efficiently APP carrying the Swedish mutation than wild-type APP (9–12). The purified enzyme catalyzes synthetic APP substrates encompassing the \( \beta \)-secretase site (9–12). Finally, Bace has an acidic pH optimum and is resistant to the aspartic protease inhibitor pepstatin A (9, 10).

Although this evidence is impressive, only limited information is available on the cell biology of Bace. Bace is an N-glycosylated transmembrane protein encoded in a 501-amino acid open reading frame, from which the first 21 amino acids correspond to the signal peptide. N-terminal sequencing of Bace purified from human brain revealed that the mature protein starts at glutamic acid 46 (10), indicating that Bace is further processed after its translocation into the endoplasmic reticulum. Other proteases, e.g. proprotein convertases (PCs) and members of the ADAM family, are also synthesized as inactive preproenzymes that require the removal of the propeptide to become active (13). It has recently been shown that pro-Bace is predominantly located in the endoplasmic reticulum and that constitutive propeptide cleavage takes place in the Golgi apparatus C-terminal to the Arg-Leu-Pro-Arg motif (14, 15), suggestive for the involvement of members of the PC family in this process. PCs are subtilisin-like serine proteases involved in the activation of many neuropeptides, peptide hormones, growth and differentiation factors, membrane-associated receptors, adhesion molecules, blood coagulation factors, plasma proteins, and some pathogenic proteins like viral coat proteins and bacterial toxins (13, 16, 17). Precursors are usually cleaved C-terminal to basic motifs like Lys/Arg-(X)-Lys/Arg, where \( n = 2, 4, 6 \) and \( X \) is essentially any amino acid but Cys and rarely Pro (13). Seven members have been thus far isolated as follows: furin, PC1 (also called PC3), PC2, PC4, PC6 (also called PC5), PACE4, and LPC (also called PC7 or PC8). All enzymes have a specific, albeit partially overlapping, expression pattern and similar but not identical substrate specificities.

Recently furin was implicated in the production of amyloidogenic peptides in familial British dementia (18, 19). This ob-

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1. The abbreviations used are: AD, Alzheimer’s disease; APP, amyloid precursor protein; IEF, isoelectric focusing; Bace, \( \beta \)-site APP cleaving enzyme; sBace, soluble Bace; Bace-ALPA, Bace in which the propeptide is mutated into ALPA (single letter amino acid code); PCs, proprotein convertases; PAGE, polyacrylamide gel electrophoresis; \( \alpha \)-PDX, \( \alpha \)-antitrypsin Portland; A\(\beta \), amyloid \( \beta \); CTFs, C-terminal fragments; WT, wild type; CHO, Chinese hamster ovary.
Generation of Neuronal Transfectants—Neuronal transfectants were obtained using calcium phosphate transfection (24, 25). Plasmids encoding APP, Bace constructs, furin, and PDX as indicated in the figure legends. In case of overnight labeling, 5% dialyzed fetal calf serum was added to the labeling medium, and starvation was omitted. For immunoprecipitation of Bace and PCs, cells were lysed in 1 ml of DIPA (50 mM Tris/HCl, pH 7.8, 150 mM NaCl, 1% saponine and chased with Dulbecco’s modified Eagle’s medium/F12 (1:1) supplemented with 10% fetal calf serum. 8–10 × 10^5 cells/10-cm² culture plate were transfected with 2 μg of DNA and 6 μl of Pugene (Roche Molecular Biochemicals) and were used for experiments the next day (CHO and RPE.40) or after 2 days (N2A and COS cells).

Radiolabeling and Immunoprecipitation—Cells (8–10 × 10^5 cells/10 cm²) were starved for 1 h in methionine-free RPMI 1640 medium and then labeled in the same medium containing 100 μCi/ml [35S]methionine and chased with Dulbecco’s modified Eagle’s medium/F12 (1:1) for the times indicated in the figure legends. In case of overnight labeling, 5% dialyzed fetal calf serum was added to the labeling medium, and starvation was omitted. For immunoprecipitation of Bace and PCs, cells were lysed in 1 ml of DIPA (50 mM Tris/HCl, pH 7.8, 150 mM NaCl, 1% Triton X-100, 1% sodium deoxycholate, 0.1% SDS). Immunoprecipitation and endoglycosidase H and F digestions were performed as described (22, 23). Immunoprecipitation of Bace and Bace mutants with either anti-Myc 9E10 or anti-Bace antibody gave identical results (data not shown). The figure legends indicated which antibody was used.

To study APP processing, cells were cotransfected with plasmids encoding APP, Bace constructs, furin, and PDX as indicated in the figures. Twenty four (for CHO and RPE.40 cells) or 48 h (N2A and COS cells) after transfection, cells were pulse-labeled for 4 h and immediately lysed. APP full-length and C-terminal fragments (CTFs) were immunoprecipitated from the cell extracts, whereas Aβ and total secreted APP (APPS) were immunoprecipitated from the conditioned medium as described (4, 24).

To discriminate between APPs originating from α- versus β-cleavage, samples from the conditional medium were resolved by 10% PAGE. Western blotting was subsequently performed with either 6E10 or 53/4 antibodies.

One-dimensional Isoelectric Focusing—Separation of Bace immuno-reactive bands in isoelectric focusing was performed essentially as described (25). Briefly, a 5% acrylamide (w/v) reducing gel containing 2% Triton X-100, 9.1 μM urea, 4% amyllopectin, pH 5–7, and 1% amyllopectin, pH 3.5–10, was run 13–16 h at a starting voltage of ~20 V/cm and a limiting voltage of 50 V/cm. Prior to IEF samples were deglycosylated with endoglycosidase F as described above.

RESULTS AND DISCUSSION

Bace Subcellular Localization in Hippocampal Neurons—We used confocal microscopy to study the intracellular localization of Bace in primary cultures of hippocampal neurons (Fig. 1). Mouse neurons indeed express Bace, and some overlap in the distribution of Bace and the Golgi marker β-COP is observed. Bace is, however, also present in β-COP negative vesicles, most
likely endosomes. Previous studies have addressed the issue of Bace subcellular distribution in non-neuronal cells using Bace overexpressed from transfected cDNA (8, 9, 12, 14, 15). Our data confirm these previous findings at the endogenous levels of expression and indicate that transfected Bace localizes to the relevant subcellular compartments. Since the levels of endogenous expression of Bace are very low (results not shown), further biochemical analysis to characterize the maturation and the activity of Bace was performed in transfected cells.

**Biosynthesis of Bace**—We next cloned and sequenced the cDNA encoding Bace from a brain-specific mouse cDNA library (Stratagene) and confirmed its identity to the sequence published by Yan et al. (11). To characterize the biosynthesis and maturation of Bace, pulse-chase experiments were performed. Transiently transfected CHO cells were radiolabeled and chased for various times (Fig. 2A). Immediately after the pulse labeling, three specific protein bands were observed as follows: a major one migrating with an approximate mass of 65 kDa and two minor ones migrating at 50 and 75 kDa, consistent with previous reports (14, 15). The 50-kDa protein disappeared during the chase, whereas the amount of 65-kDa protein toward a 65- and 75-kDa protein. The mobility of endoglycosidase H-resistant (endoH) Bace, as well as the deglycosylated Bace are indicated by arrows. B, immunoprecipitated Bace was either untreated (–) or treated with endoglycosidase H (H) or N-glycosidase F (F). C and D, no major differences in glycosylation (C) or secretion (D) of the Bace-ALPA mutants are observed. The positions of the molecular weight markers are indicated.

![Figure 2: Biosynthesis of Bace](image)

Fig. 2. **Biosynthesis of Bace.** CHO cells were transfected with empty vector (–), Bace cDNA (B), Bace-ALPA cDNA (BALPA), or the soluble variants (sB and sBALPA), radiolabeled for 1 h, and either chased for the times indicated (A and B) or for 4 h (C and D). Bace from cell lysates (A–C) or medium (D) was immunoprecipitated with monoclonal antibody 9E10 and analyzed on SDS-PAGE. A, pulse-chase experiment indicating the conversion of a 50-kDa protein toward a 65- and 75-kDa protein. The mobility of endoglycosidase H-resistant (endoH) and endoglycosidase H-sensitive (endoH) Bace, as well as the deglycosylated Bace are indicated by arrows. B, immunoprecipitated Bace was either untreated (–) or treated with endoglycosidase H (H) or N-glycosidase F (F). C and D, no major differences in glycosylation (C) or secretion (D) of the Bace-ALPA mutants are observed. The positions of the molecular weight markers are indicated.
should not react with mature sBace and which, in fact, failed to recognize the bands generated in the presence of furin (Fig. 3B). The heterogeneity of the bands corresponding to mature sBace is commonly observed with other proteins in IEF (25). This can be explained by the heterogeneity in the glycosylation pattern of sBace together with the asparagine to aspartic residue conversion that occurs during the deglycosylation prior to IEF. Similar results were obtained with full-length Bace. Upon furin cotransfection part of pro-Bace was converted to the mature Bace form (Fig. 3, C and D; see also Fig. 5, A and C). The fastest migrating band in Fig. 3C could be immunoprecipitated by antibodies directed against mature Bace but not by antibodies directed against the propeptide (D). This indicates that this band represents processed Bace. We observed, however, that a fraction of pro-Bace was resistant to furin treatment (indicated as pro-Bace$^{nFur}$). Based on the pulse-chase experiments shown in Fig. 2, from which it is clear that a large part of wild-type Bace remains endoglycosidase-sensitive after 4 h of chase, we conclude that this fraction represents newly synthesized, immature glycosylated Bace. Since this pool is localized in the early compartments of the secretory pathway, it is not accessible for furin, which is only active in the late Golgi apparatus. The fraction of protein that is labeled Pro-Bace in Fig. 3, C and D, on the other hand, represents the fully glycosylated protein that has reached the Golgi compartment and is therefore sensitive to furin cleavage. To our surprise, both sBace–ALPA and Bace–ALPA are efficiently processed in RPE.40, furin-deficient cells (Fig. 3), and their processing is not inhibited by the PC inhibitor a1-PDX (not shown) in contrast to their wild-type Bace counterparts. Furthermore, preliminary results using protease inhibitors indicate that this cleavage is performed by a trypsin-like protease (data not shown). It is therefore likely that the double ALPA mutation creates a novel site that becomes artificially cleaved by a non-PC, trypsin-like protease. Regardless of the identity of this protease and the precise site of cleavage, it is clear that this processing event is physiologically irrelevant.2 In any event, the fact that wild-type Bace (Bace-WT) and “wild-type” sBace are poorly cleaved in furin-deficient cells, together with the rescue of the cleavage process after furin expression, indicates strongly that furin is involved in pro-Bace maturation in vivo. That other members of the PC-family could rescue the cleavage of Bace-WT cannot, however, be excluded. Therefore, all other PCs that have broad tissue distribution, i.e., PACE4, PC6 (isofoms A and B), and LPC, were tested for their activity in sBace (Fig. 4) and Bace (Fig. 5) maturation. Expression of the enzymes was confirmed (Fig. 5B). From Fig. 4, it is obvious that only furin was able to process pro-sBace. Furthermore, endogenous processing activity on pro-sBace was observed in CHO cells (right panel) but not in RPE.40 cells (left panel), and activity could be stimulated by expression of furin and inhibited by expression of the PC inhibitor a1-PDX. a1-PDX is a genetically engineered serine protease inhibitor derived from the trypsin inhibitor a1-antitrypsin and has been shown to inhibit efficiently furin and to a lesser extent PACE4, PC6A, and PC6B (26, 27). The same experiment was performed with wild-type Bace (Fig. 5). Although overexpression of furin resulted in efficient processing of pro-Bace, other PCs were capable of cleaving pro-Bace to a various extent as well. This is unlikely to be a cell type-specific effect, since similar results were obtained in the neuron-based cell line N2A (Fig. 5C). On the other hand, the data obtained with sBace suggest that furin has a preponderant role in pro-Bace processing in vivo.

APP Processing by Wild-type and Mutant Bace—To determine whether the prodomain cleavage and membrane anchoring of Bace affect g-secretase activity, RPE.40 cells were cotransfected with plasmids encoding APP, wild-type Bace, Bace–ALPA, sBace, sBace–ALPA, and furin or a1-PDX as indicated in Fig. 6 (A–C). Processing of APP was analyzed by in vivo labeling and immunoprecipitation of cell-associated C-terminal fragments (CTFs, Fig. 6A), total secreted APP (APPs, Fig. 6B, bottom), and aB peptides (Fig. 6B, top) or by Western blotting to discriminate between APPsα and APPsβ generated by a– and β–secretase, respectively (Fig. 6C). Expression in RPE.40 cells of APP alone resulted in cleavage of APP mainly at the

2 We have recently made a single amino acid substitution into the PC consensus cleavage site RLPR of Bace to generate a GLPR site. This mutant is not processed, in agreement with our hypothesis that the wild-type Bace is processed by a member of the PC family, whereas the ALPA mutant creates an artifactual cleavage site.
**α-secretase site**, as shown by the accumulation of CTFs starting at the α-cleavage site (Fig. 6A) and by the fact that most of the secreted APP corresponded to APPsα (Fig. 6C, lane 1). β-Stubs (Fig. 6A) and APPsβ (Fig. 6C), on the other hand, were almost undetectable, which is entirely consistent with data obtained in many other cell lines showing that endogenous β-secretase activity is very low, and APP processing is mainly by the non-amyloidogenic pathway in non-neuronal cells (28).

Coexpression of Bace induced cleavage of APP at the 2 β-secretase sites (Asp1 and Glu11 (9)), with the expected concomitant decrease in α-processing (Fig. 6, A and C). Competition between α- and β-secretase for the substrate APP has been reported previously (9–11, 29–31). It is remarkable that CTFs (Fig. 6A) and secreted peptides (Fig. 6B) starting at position Glu11 are far more abundant than those starting at Asp1 under the experimental conditions used. The phenomenon is not specific for RPE.40 cells, since similar results were obtained with N2A and COS cells (Fig. 6D). We speculated that Asp1 is still the preferred β-secretase site under those conditions but that the 99 amino acids CTF that is generated by Asp1 cleavage (CTFβ1) can be further processed by overexpressed Bace to yield the Glu11 C-terminal APP fragment (CTFβ11). That this interpretation is correct was proven by two different experiments. First, if Bace cleaves preferentially at Asp1, then APPs secreted into the medium should react with an antibody that specifically recognizes the neoepitope generated after Asp1 cleavage. As shown in Fig. 6C, Bace transfection indeed resulted in the substantial accumulation of secreted APP that contains this neoepitope (APPsβ). Second, if the relative abundance of Glu11 cleavage in our experiments is a consequence of the high levels of Bace expression, then decreasing Bace expression should result in a switch toward Asp1 cleavage. This is, in fact, what we observed (Fig. 7). Transfection of N2A cells with decreasing amounts of Bace cDNA resulted in decreasing levels of Bace protein expression (Fig. 7A, 2nd panel). Immunoprecipitation of peptides secreted into the medium showed that at high levels of Bace protein (1 μg of transfected cDNA) most of the secreted Aβ peptides starts at Glu11, whereas with decreasing Bace expression levels (until they are undetectable in our assay) the majority of the secreted peptide starts at Asp1 (Fig. 7A and quantification in B). As expected, there was a direct correlation between the levels of Bace expression and the amount of APPsβ recovered in the medium, and decreasing levels of APPsβ were accompanied by increases in the amount of secreted APPsα (Fig. 7A, two lower panels). Altogether, these results show that the cleavage at Glu11 is a function of the

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### Table: Processing of sBace by PCs

| sBace | PC | CHO |
|-------|----|-----|
| -     | +  | +   |
| +     | -  | +   |
| Fur   | PACE4 | PC6A | PC6B | LPC | α1-PDX |
|       |       |       |       |     |         |

**Fig. 4. Processing of sBace by PCs.** CHO and RPE.40 cells were transfected with empty vector (−), sBace alone, or together with furin (Fur), PACE4, PC6A, PC6B, LPC, or α1-PDX and radiolabeled overnight. Cell culture medium was incubated with anti-Bace antibody and analyzed on IEF slab gels. The position of sBace and pro-sBace is indicated.

**Fig. 5. Processing of Bace by PCs.** CHO (A), RPE.40 (A–C), and N2A (C) cells were transfected with empty vector (−), Bace alone, or together with furin (Fur), PACE4, PC6A, PC6B, LPC, or α1-PDX. Cells were radiolabeled overnight (B) or for 1 h followed by 4 h of chase (A–C). Cell lysates were incubated with anti-Bace antibody (A–C) or antibodies directed against specific PCs (B) and analyzed on IEF slab gels (A–C) or SDS-PAGE (B). Pro-Baceβ11 and pro-Bace refer to the furin-resistant and -sensitive bands, respectively (see text). The asterisk indicates an unspecific protein band.

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**Processing of Bace by Proprotein Convertases**

4215

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expression level of Bace. The Glu11 position is known to be a normal cleavage site of Bace (see for example Vassar et al. (9)). Moreover, peptides starting at this position are produced by primary cultures of neurons and are also present in plaques of AD patients (Ref. 28 and references therein). We therefore consider the Glu11 cleavage as a reliable reflection of the Bace activity in our experimental system. In addition we analyzed also the production of APPβ1, which reflects cleavage of APP at Asp1. Our approach therefore allows us to evaluate the proteolytic capacity of Bace at position Glu11 as well as at position Asp¹ and therefore to determine whether propeptide processing is needed for Bace activity or not. In this regard, processing of APP was observed even in the absence of furin, suggesting that pro-Bace is an active enzyme (Fig. 6, A–C). RPE.40 cells lack furin, and little or no mature Bace is detected after overexpression (Fig. 5A, lane 2). Since other PCs, at least when overexpressed, can cleave pro-Bace (Fig. 5), one could argue that enough mature Bace is synthesized in RPE.40 cells that would explain the observed processing of APP. Although we cannot definitively rule out this possibility, we consider this as very

**Fig. 6. Processing of APP by Bace and Bace mutants.** RPE.40 (A–C), N2A (D), and COS (D) cells were transfected with plasmids encoding APP, Bace, furin or α-PDX as indicated at the top of the figures. Twenty four (for RPE.40 cells) or 48 h (for N2A and COS) after transfection, cells were labeled for 4 h and lysed. A, CTFs and full-length APP immunoprecipitated from cell lysates. B, immunoprecipitation of APPs and APPβ from the conditioned medium. C, Western blotting using antibodies 6E10 (top) and 53/4 (bottom) specific for α-secretase-cleaved APPs (APPα) or β-secretase-cleaved APPs (APPβ) at the Asp¹ site on samples from the conditioned medium. D, immunoprecipitation of CTFs (upper panel), APP (middle panel), and Bace (lower panel) from N2A (left) and COS (right) cells that have been cotransfected with APP and different Bace constructs, as indicated at the top. Bace; BALPA, Bace-ALPA; sβ; sBace; sBALPA, sBace-ALPA; β1, CTF or ββ starting at Asp¹; β11, CTF or ββ starting at Glu¹11; α, CTF starting at the α-cleavage site.

**Fig. 7. Effect of Bace expression level on Asp¹ and Glu¹1 cleavage of APP.** N2A cells were cotransfected with 1 µg of APP-encoding plasmid and the indicated amounts of Bace-encoding plasmid (each transfection was with 2 µg of total DNA; empty vector was used to complete this amount). A, cells were metabolically labeled, and the secreted peptides (upper panel) and Bace (second panel) were immunoprecipitated. A fraction of the conditioned medium was analyzed by Western blotting to detect APPα and β forms (lower two panels). B, PhosphorImager quantification of the bands shown in the upper panel of A. 1 and 11 refer to the start position of the Aβ peptide.
unlikely, since coexpression of α,-PDX, that inhibits several other PCs in addition to furin, resulted in no detectable decrease in β-secretase cleavage as compared with Bace or Bace plus furin (5th lane versus 3rd and 4th in Fig. 6A). Moreover, in preliminary experiments, we found that when Bace is retained in the endoplasmic reticulum by means of a KK motif, it is still capable of cleaving APP (not shown). This Bace-KK is, as expected, not complex glycosylated. Since propeptide cleavage occurs in the Golgi and trans-Golgi network, this mutant Bace-KK protein should still contain its propeptide.

The BACE-ALPHA mutant is, as expected, as active as wild-type Bace in cleaving APP (Fig. 6, A and B). Expression of sBace, finally, induces cleavage of APP mainly at position Asp1 when overexpressed in vivo suggests that sBace is less efficient in reaching the APP substrate or at least the Asp1 site (9) and that the transmembrane domain of Bace is needed to allow for efficient cleavage at the Glu11 site.

In conclusion, we confirm and extend previous work that pro-Bace is processed by furin to its mature form. There is redundancy in the proteolytic maturation of Bace, since other members of the PC family can compensate for loss of furin activity. We present evidence suggesting that this maturation step is not essential for the β-secretase activity of Bace on APP. We conclude that the maturation of pro-Bace has little relevance as a therapeutic target for Alzheimer's disease. Several other functions, apart from inhibiting proteolytic activity of the proenzymes, have been found for propeptides, including roles in folding and intracellular transport. Possibly the propeptide of Bace is important for folding or intracellular transport of pro-Bace. Alternatively, it is possible that APP is not the only physiological substrate of Bace and that cleavage of other yet unidentified Bace substrates is dependent on appropriate removal of the propeptide.

Finally, our finding that pro-Bace is able to cleave APP implies that it could be active as a β-secretase in early biosynthetic cell compartments, i.e. in endoplasmic reticulum and early Golgi. Therefore, it is likely that pro-Bace is involved in the generation of the intracellular amyloid peptide pool as well (32–35). This pool is considered by some investigators as the real culprit in Alzheimer's disease.

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Addendum—While this work was under revision, a paper by Benett et al. (37) suggested that furin is responsible for the proteolytic removal of the propeptide from Bace.
Processing of β-Secretase by Furin and Other Members of the Proprotein Convertase Family
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