## Phylogeny

Hormonally up-regulated neu tumor-associated kinase (HUNK) is a serine/threonine protein kinase most closely related to the SNF1/AMPK family (Hormonally up-regulated neu tumor-associated kinase [HUNK], 2006, pp. 23-24, 31-32; Ramos-Solís et al., 2022, pp. 1-2). Sequence comparisons place HUNK on a distinct branch of this family, outside the best-defined SNF1/AMPK sub-families (HUNK, 2006, pp. 31-32). Murine and human proteins share ~95 % identity (HUNK, 2006, pp. 29-30). The Manning et al. (2002) kinome classification groups HUNK within the CAMK clade, and motif-based clustering positions it near CAMK/NEK kinases (Johnson et al., 2023, pp. 4-5).

## Reaction Catalyzed

ATP + L-seryl/threonyl-[protein] ⇌ ADP + H⁺ + O-phospho-L-seryl/threonyl-[protein] (HUNK, 2006, pp. 23-24, 37-38; Manning et al., 2002).

## Cofactor Requirements

Requires ATP and divalent cations Mg²⁺ or Mn²⁺ for catalysis (HUNK, 2006, pp. 23-24, 39-40; Characterization of a Novel HUNK Inhibitor, 2024, pp. 58-63).

## Substrate Specificity

A universal consensus motif has not been defined (Characterization of a Novel HUNK Inhibitor, 2024, pp. 58-63). In a kinome-wide peptide screen, HUNK showed high activity toward PDHA1 Ser293 (motif RYHGHSMSDP; 98.86 percentile, ranked 7 of 217 kinases) (Johnson et al., 2023, pp. 21-23).

## Structure

The human protein comprises 714 aa (~80 kDa) with an N-terminal region, a central 260-aa catalytic domain, and a C-terminal region that contains a ~45-aa SNF1 homology (SNH) domain (HUNK, 2006, pp. 30-32). Canonical serine/threonine kinase motifs (e.g., DLKPEN) are present, whereas tyrosine-kinase-specific residues are absent (HUNK, 2006, pp. 29-30). A basic patch within the kinase domain matches a PIP₂-binding consensus (Targeting HUNK to Suppress Autophagy, 2019, pp. 26-32). No experimental 3-D structure is available; homology and AlphaFold models predict the usual bi-lobed kinase fold with regulatory C-helix, activation loop, and hydrophobic spine (Targeting HUNK to Suppress Autophagy, 2019, pp. 51-57; Characterization of a Novel HUNK Inhibitor, 2024, pp. 58-63).

## Regulation

Documented post-translational modifications include phosphorylation (S65, S360, S368, Y378, S561, S585, T618), acetylation, carboxylation, and glycosylation; upstream enzymes and functional consequences remain undefined (Characterization of a Novel HUNK Inhibitor, 2024, pp. 58-67). The C-terminal SNH domain is proposed to auto-inhibit kinase activity (HUNK, 2006, pp. 31-32). Hormonal and oncogenic cues up-regulate expression: 17β-estradiol, progesterone, HER2/neu, and Akt (HUNK as an Immune Regulator, 2024, pp. 39-44; Ramos-Solís et al., 2022, pp. 1-2). Kinase-inactive mutant K91M diminishes tumor growth and alters subcellular localization (Targeting HUNK to Suppress Autophagy, 2019, pp. 39-43). HUNK interacts with the Nedd4 E3 ubiquitin ligase, but ubiquitination sites on HUNK have not been mapped (Characterization of a Novel HUNK Inhibitor, 2024, pp. 63-67).

## Function

HUNK influences cell survival, proliferation, autophagy, and metastasis (Ramos-Solís et al., 2022, pp. 1-2). Adult mouse expression is notable in ovary, lung, brain, mammary gland, uterus, and prostate and is developmentally regulated (HUNK, 2006, pp. 31-32, 39-40). Reported substrates include EGFR Thr654, Rubicon Ser44/Ser92, ITM2A Thr35, GEF-H1 Ser645, AGAP3 Ser396, histone H1, and myelin basic protein (HUNK, 2006, pp. 39-40; Characterization of a Novel HUNK Inhibitor, 2024, pp. 63-67; Ramos-Solís et al., 2022, pp. 1-2). Non-substrate partners comprise Nedd4, the Beclin-1 complex, cofilin-1, and Rabaptin-5 (Characterization of a Novel HUNK Inhibitor, 2024, pp. 63-67; HUNK as an Immune Regulator, 2024, pp. 39-44; Targeting HUNK to Suppress Autophagy, 2019, pp. 39-43).

## Inhibitors

Staurosporine inhibits HUNK activity (Ramos-Solís et al., 2022, pp. 1-2), although one report claims no dedicated pharmacological inhibitors are currently available (Targeting HUNK to Suppress Autophagy, 2019, pp. 39-43).

## Other Comments

HUNK is frequently over-expressed in HER2+ and triple-negative breast cancers, correlating with poor prognosis and contributing to metastasis and drug resistance (Ramos-Solís et al., 2022, pp. 2-4; HUNK as an Immune Regulator, 2024, pp. 39-44). Somatic alterations are uncommon (~1.3 %), but include kinase-domain missense mutations, copy-number gains, and fusions (HUNK-MRAP, EVA1C-HUNK) (Ramos-Solís et al., 2022, pp. 2-4). The human HUNK gene maps to chromosome 21q22, a locus linked to Down syndrome and Alzheimer’s disease (HUNK, 2006, pp. 29-30).

## 9. References

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