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Summary

N-TERMINAL MYRISTOYLATION PREVENTS DEGRADATION OF SRC-FAMILY KINASES VIA DUAL N-DEGRON PATHWAYS TARGETING FREE AND ACETYLATED GLYCINE RESIDUES

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A dual N-degron surveillance mechanism targeting non-myristoylated Src-family kinases involves CUL2-ZYG11B/ZER1 recognition of free glycine residues and DCAF10-DDB1-CUL4A recognition of aberrantly acetylated glycine, offering potential therapeutic targets in colorectal and other cancers.

KEY POINTS

- Src-family tyrosine kinases are mutated or aberrantly regulated in up to 80% of colorectal cancers and are central drivers of oncogenic signaling, but have proven difficult to target therapeutically.
- Loss of N-terminal myristoylation leads to increased SFK turnover through two parallel degradation pathways: CUL2-ZYG11B/ZER1 recognizes free N-terminal glycine residues, while DCAF10-DDB1-CUL4A targets aberrantly acetylated glycine-2.
- Knockdown of DCAF10 stabilized acetylated Lyn in cells, and in vitro assays confirmed direct recognition and ubiquitination of acetylated glycine substrates by the DCAF10-DDB1-CUL4A complex.
- Only wild-type myristoylated Lyn was stable and correctly localized to membranes in re-expression experiments, while non-myristoylated or G2A-mutant forms were typically N-terminally acetylated and accumulated in the nucleus when export was blocked.
- DCAF10 expression correlates with patient outcome in ovarian and lung cancer, and these N-degron quality control pathways may represent new therapeutic entry points for targeting oncogenic SFK signaling.

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