



SPRING 2021

**Biochemistry and Molecular Biology
Brown Bag Series**

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M.S. Student

***"The F-box protein FBW7 negatively
regulates the stability of ERK3 protein"***

Tuesday, February 2, 2021

11:00 AM

**Please contact x3249 if you would like to attend but
did not receive an emailed link.**

Lab: Weiwen Long, Ph.D.



<https://science-math.wright.edu/biochemistry-and-molecular-biology>

Abstract

The F-box protein FBW7 negatively regulates the stability of ERK3 protein

Extracellular signal-regulated kinase 3 (ERK3) is a member of the atypical mitogen-activated protein kinase (MAPK) subfamily, which has been shown to play important roles in a variety of cellular processes such as proliferation, differentiation, migration and apoptosis. While the signals for regulating ERK3 kinase activity are still unclear, ERK3 is known to be an unstable protein whose function is tightly regulated by ubiquitination and proteasomal turn over. The deubiquitinating enzyme USP20 has been shown to regulate ERK3 by stabilizing the kinase, but presently, no ubiquitin ligases have been identified. The SKP1-CUL1-F-box protein (SCF) E3 ligases are a subfamily of ubiquitin E3 ligases that are composed of the adaptor protein SKP1, the scaffold protein Cullin1 (CUL1) and a specific F-box protein. As a component of the SCF-E3 ligase complex, the F-box protein recruits specific substrates to the E3 complex via its substrate interaction domain. Many substrates of SCF-E3 ligases contain a so-called phosphodegron, a phosphorylated consensus motif S/TXXXS/T that is recognized by F-Box proteins such as FBW7 and Beta-TRCP. Interestingly, ERK3 protein sequence contains multiple potential phosphorylated S/TXXXS/T motifs. As such, a siRNA screening was performed to identify F-box protein(s) that regulates ERK3 protein level. Knockdown of FBW7 was found to lead to a remarkable increase of ERK3 protein level, suggesting FBW7 negatively regulate ERK3 protein level. This is confirmed by the finding that overexpression of FBW7 led to a great decrease of ERK3 protein level. Further, we have demonstrated that FBW7 downregulates ERK3 protein stability depending on its F-Box domain. To determine which domain of ERK3 is important for the regulation by FBW7, we generated several ERK3 deletion mutants. We found that the presence of N-terminus is required for the destabilization of ERK3 by FBW7, implying the phosphodegron of ERK3 is in the N-terminus. Taken together, these results demonstrate that FBW7 negatively regulates ERK3 protein stability. In our future work, we will determine whether SCF-FBW7 polyubiquitinates ERK3 and identify the phospho-degron(s).

