

## **SUPPLEMENTAL MATERIAL**

### **An FTS/Hook/p107<sup>FHIP</sup> complex interacts with and promotes endosomal clustering by the Homotypic Vacuolar Protein Sorting (HOPS) Complex**

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**Contents: Supplemental Figures S1-S7.**

## Figure Legends

### Figure S1. Characterization of the Hook/FTS interaction.

Sequence alignment of human and Drosophila Hook proteins, depicting the predicted coiled-coil region (indicated by green “C”) and the C-terminal helical region (indicated by red “H”). The indicated sequences were aligned using ClustalW2 (<http://www.ebi.ac.uk/Tools/clustalw2/index.html>) and displayed using Boxshade ([http://www.ch.embnet.org/software/BOX\\_form.html](http://www.ch.embnet.org/software/BOX_form.html)).

### Figure S2. Characterization of the Hook/FTS interaction.

(A) Anti-Flag immune complexes were prepared from HEK293T cell extracts or from HEK293T/Flag-HA-FTS cells and these complexes along with crude lysates subjected to immunoblotting using the indicated antibodies. FTS was found to interact with Hook1, Hook2, and Hook3, confirming the results of mass spectrometry.

(B) Anti-FTS antibodies immunoprecipitate Hook1 and Hook3. Lysates from HEK293T cells were subjected to immunoprecipitation using the available FTS antibodies which IP only poorly. Nevertheless, Hook1 and Hook3 were detected in these immune complexes (lane 3) but not in control complexes (lane 2).

(C) FTS protects Hook1<sup>657-728</sup> from degradation via the proteasome. The indicated Hook1 proteins were expressed alone or in combination with GST-FTS. Prior to harvesting, cells were incubated with MG132 (20  $\mu$ M, 8 h) prior to analysis of lysates by immunoblotting. As expected, Hook1<sup>657-728</sup> was readily detected in extracts from cells expressing GST-FTS independent of the presence of MG132. In contrast, Hook1<sup>657-728</sup> was absent when FTS was not co-expressed but was present under these conditions when MG132 was added. These data indicate that FTS protects this C-terminal fragment of Hook1 from turnover through the proteasome.

(D) Immunoblotting of extracts demonstrates depletion of the indicated proteins by RNAi. Cells were transfected with the indicated siRNAs and after 72 h, extracts were subjected to immunoblotting with the indicated antibodies.

**Figure S3. Multi-sequence alignment of p107<sup>FHIP</sup> and related proteins.**

(A) The indicated sequences were aligned using ClustalW and displayed using Boxshade.

(B) Analysis of p107<sup>FHIP</sup> for coiled-coil regions using the Coils Server at [www.ch.embnet.org/software/COILS\\_form.html](http://www.ch.embnet.org/software/COILS_form.html).

**Figure S4. Depletion of FTS reduces the ability of Vps18 to promote late endosome/lysosome clustering.**

(A) HeLa cells were transfected with control siRNA or siRNA targeting the indicated gene. After 48 h, cells were transfected with GFP-Vps18 and 60 h later, late endosomal/lysosomal clusters were examined immunofluorescence using anti-LAMP1 antibodies in conjunction with detection with Alexa598 conjugated secondary antibodies (red). GFP-Vps18 was identified by GFP fluorescence. In order to determine the integrated intensity for LAMP1 within clusters, a threshold (+ Threshold) was applied such that the maximal pixel signal was in the linear range. In the absence of threshold (- Threshold), individual vesicles not present within clusters can be seen in cells wherein the indicated gene was targeted for depletion. Two independent siRNAs were used for each gene.

**Figure S5. The frequency of cells displaying LAMP1 staining intensity greater than 10,000 pixels within the GFP-Vps18 cluster is reduced upon depletion of FTS, Hook, and p107<sup>FHIP</sup> proteins.**

(A) HeLa cells were transfected with control siRNA or siRNA targeting the indicated gene. After 48 h, cells were transfected with GFP-Vps18 and 60 h later, late endosomal/lysosomal clusters were examined immunofluorescence using anti-LAMP1 antibodies in conjunction with detection with Alexa598 conjugated secondary antibodies (red). GFP-Vps18 was identified by GFP fluorescence. In order to determine the integrated intensity for LAMP1 within clusters, a threshold (+ Threshold) was applied such that the maximal pixel signal was in the linear range. In the absence of threshold (- Threshold), individual vesicles not present within clusters can be seen in cells wherein

the indicated gene was targeted for depletion. The cumulative number of cells displaying the indicated pixel intensity is shown. Two independent siRNAs were used for each gene.

**Figure S6. Overexpression of FTS or Hook proteins induces late endosome/lysosome clustering.**

(A) HeLa cells were transfected with plasmids expressing GFP, GFP-FTS, Flag-Hook1, Flag-Hook2, or Flag-Hook3. After 60 h, cells were fixed and stained with Lamp1 antibodies as described in Figure 6 legends.

(B) Percentages of transfected cells displaying clear Lamp1 clusters were counted. The mean +/- SEM of two independent experiments is indicated.

**Figure S7. Components of the FHF complex are required for efficient decay of internalized EGF.**

(A-E) Kinetics of Rhodamine-EGF decay in cells lacking FHF complex components. HeLa cells were transfected with the indicated siRNA and EGF decay measured as follows using the previously published assay [J. Cell Biol. 157, 91-101 (2002)]: HeLa cells were serum-starved for 2 hours and treated with 500 ng/ml Texas Red conjugated EGF (EGF-TR) on ice. Cells were left on ice for 15min and then transferred to 19.5°C to initiate the internalization and incubated for 1 hour prior to washing the cells with PBS. Cells were then transferred to 37°C to initiate EGF transit through the endocytic system. At the indicated times, cells were imaged using fluorescence microscopy at the same

settings. Threshold was set using cells not treated with Rhodamine-EGF and cells with at least two Rhodamine-positive punta that exceed the threshold were counted as EGF positive using Metamorph software. In panels B and C, the indicated siRNA-resistant expressed vectors were transfected and transfected cells (based on GFP) counted. (A-D) The percentage of EGF positive cells over total cell numbers were plotted. (E) Images of control, siFTS, and siFTS/FTS rescue vector cells over the timecourse are shown.

# Xu et al, 2008 Figure S1

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Hook1      1  MEETQPPPPQPCFLKLCSSLTINLWLOTFTNTASPCQDVKQLTSGVAMAQVLEQIDAFAWFSNWSLRIKE--DVGDNRWRLKASNLKVKVLOGHSVYY
HOOK3     1  MFSVES--LEAEALCSSLTINLWLOTFTNVDAPCQTVEDLTINGVVMAQVLEQIDPAVLEAEWLRIRIKT--FVGDNRWRLKASNLKVKLTKGLLDYN
Hook2     1  MS-----MKAELCCSLLTINLWLOTFTNVPSPASPCDLSGCAVAVYLNQIDFSWFNEAWLOGISE--EGGNWRLKVKVLSLKLVSIVSVEYS
Dm hook   1  -----MSAPKNEMYYSLLEWFKFTININAFHADAEALADGVALAACLNGFAEESFDIAWLSIKIRASAVGSNWRLRMSNLKVKVLSVYYDY
consensus 1  .

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HOOK3    88  HFFLQQQINQITLPDNLNLTGESHDAELGRMLQLLGCALNCEKQKQBYICAIMYVESVQHVWVMTAIOELMSKSEVSVAGNDAYVLDRC
Hook2    84  QVILAHFNSAEHLDPDNLISLIGESDPAELGLLQLLGCALNCEKQKHNTMTLLESVQHVWVMTAIOELMTKIDTDSLSPTTYGNFSSQ
Dm hook   85  SIVLYNYSLSDFSKPDLGRIRIENCDLELEIRLLQLLGCALNCAKCKQSYITETIMCLEBBIICANIMRAIOELIATRQASTEGGVVASSLSRG
consensus 91  .

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HOOK3    178  LAKTITTEENLALSAKBEIQAORCEBBLMQVAVLQBEKSSLAARNOVBERLNGSD-----SIDPNSPAGRRHLOLOLOLEBQLQBE
Hook2    174  SRRYYFLSEBAEGBELQRCQDLEMLLSEKQSLAENAGLERMGRPE-----GETPTGLIAKLLLOSOLBQLQBE
Dm hook   175  SRTGLLESKAVQEBREALAQCKEFTKPKLLLDKIKNLQELHLKLEQFRRLEQHSVTIGDDGVSLGIVQTSVAVYNEERLQLELKEE
consensus 181  .

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HOOK3    258  TFRLEAAKDDYRIRCEBLEKBLSEFRQNDLTLTADBAQSLKDEIDVLRHSSDRVSKLBEQVESYAKKLEDGLDRNRQVKLLEBENWY
Hook2    252  NFRLESGREDRIRCEBLEBEVWALQHRNQLTSLAQAALQKDEMDLROSSERAGGLEATITSCRRRCELEBRLRQVQLBERNAGH
Dm hook   265  LLOSEGAREDKIQAQQDLDLHQMQRLEBELMKSSEVITLKDVEDVLRBSNDKIKTCEALDITYKKLEDYNDLKKQVKLEBRSAPY
consensus 271  .

Hook1    351  MENTVSLBEBLKANAARSOLETYKROVDLHVLKSSBSKADLAFVWKRLEEKHEALKEKRLRIBORDLKEPNEELRCSOVQODHL
HOOK3    348  MONTVSLBEBLRKANAARSOLETYKROVWHLQNLSEBSKADKLFDFYRRLKRYVLSLOKEKRLRTERKDSLETTIIBELRQVQABGQL
Hook2    342  ABRIRQLELELRAGSLRAQLBAQRROVQVLOSQCEBAMKAERKWLFECSNLEBRYVESVYKKEKRLLABRDSLREBANBELRCAQOLQPRGL
Dm hook   355  VCCNAQFEELAKRYANTKGVQVLEKKELEQDLRAKLDABSSKNVLEFIDKNNLESKNLALQAKSLIKKEDNLEAVDELKCSQLESSN--
consensus 361  .

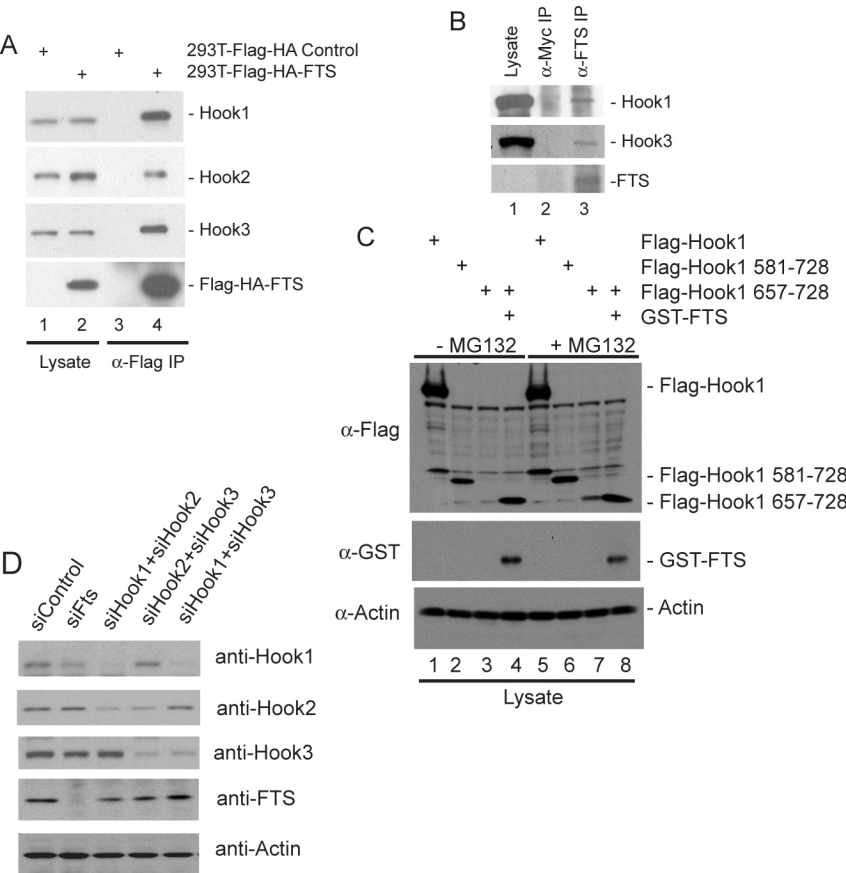
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HOOK3    438  ITQGLMPLPQOESSDLAAEIVTPEIREKLRLOHENKMLRLNQBGSNDKIALQSLLDANLEKNELETBRNLRNORLEWQSOVELE
Hook2    432  TQADPSLDFTSTPEVDNLAABIEMAEERELRLQENKRCRQENADRREBELQELQKHFMNELETERLSKBRIRRELOOEDL
Dm hook   443  -----HALGTTVSRBEIESTATVEKLRLEAENKALRECGSQ-----TALAQLDDANKRCBNLEQLKTANERLISLSHASQSD
consensus 451  .

Hook1    528  QKSLQEQGSKSEBSSSKLRKLEBAHEKLEIVHHELOKQKRELEIDLOEDINON-VQNTBELBAALQKKBEDMKAMBERRYKYLEKARNV
HOOK3    528  QKSLQEQGSKL-ABDSVLLKLEBHLKLEHANNELQKRALEIDLEERFANS-SLKTEBELBALRKBEBMKOMBERRYKYLEKASV
Hook2    521  QKALQEQGSKTEDAISLLKRLKLEBHLKLEHAEDELQKREYIELEEPTDSSSTARIEBELQHNLOKKAADLRAMEERYRYVVKARV
Dm hook   519  DPIIK-----SEFQKQIKQMLNBOITQLBEAVTQSTSLQCKVTOLEBTLNLSARQQLVLYDAKRYKQVEKAKV
consensus 541  .

Hook1    617  IKTLDPKINE--ASAEIMLRKQLABKERRTILESECKVAKFRDYEBEKLIVSAWYKSLAQKLGESRLVSGGACSDTGACTPDR
HOOK3    615  IRTLDPKQNE--AAPPIALNQLQCBDRDLFLESLEBEFKTSQREMEBKYSVSAWYMGMTLTKKAABDRLASG-----SGQ
Hook2    611  NCTBPKQRFACAPPFHSRLRQLREKLDVIRLELWDFKTSQRECBKLLSAWYMGMALQKAGEBRAPAH-----C
Dm hook   591  IKSIDPIIAS-----ALDASYLEKADIVBEBPKP---KMSWBEQLTSAFYRUGMNAQRDIDSKLAILMG-----SGQ
consensus 631  .

Hook1    703  SFLAQQRHINTTRNLSVKVPATISD----
HOOK3    693  SFLARQRCATISRRSYFCHVQPADAR----
Hook2    689  SFLAQQRHATNRRRGPGRDASLNLRPTDKH
Dm hook   659  TFLARQRCAPRISLSAMSK
consensus 721  .

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Xu et al, 2008 Figure S3A

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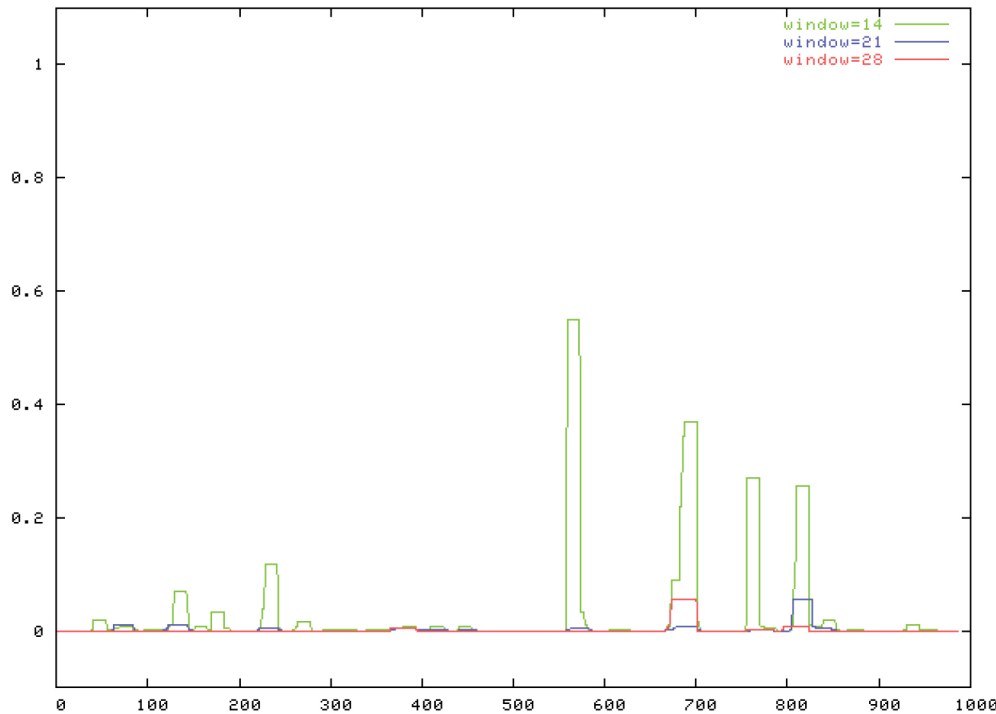
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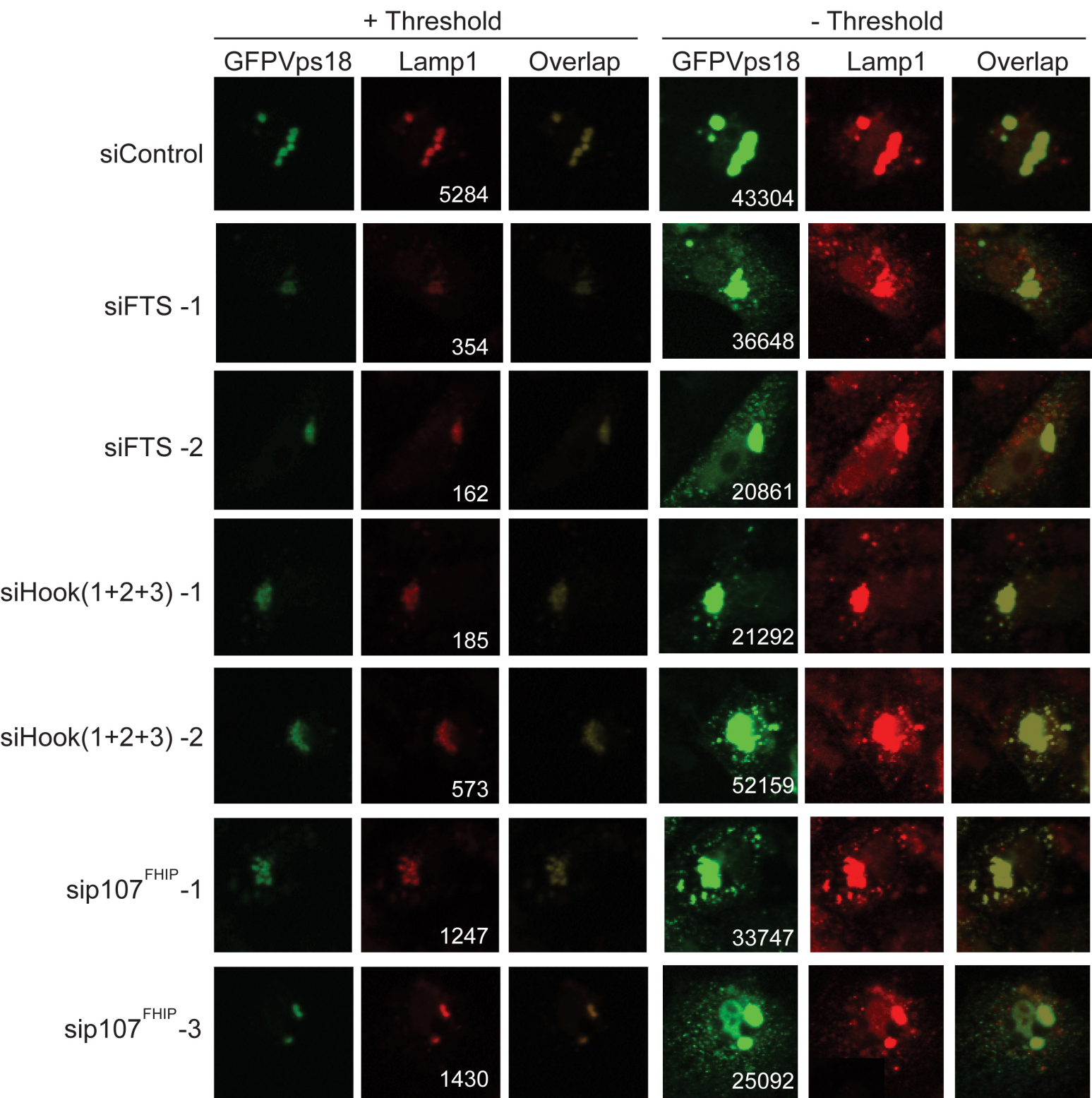
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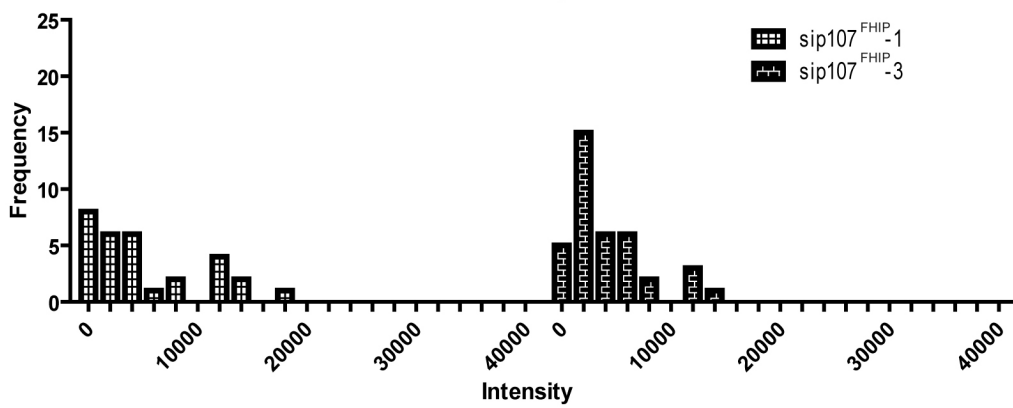
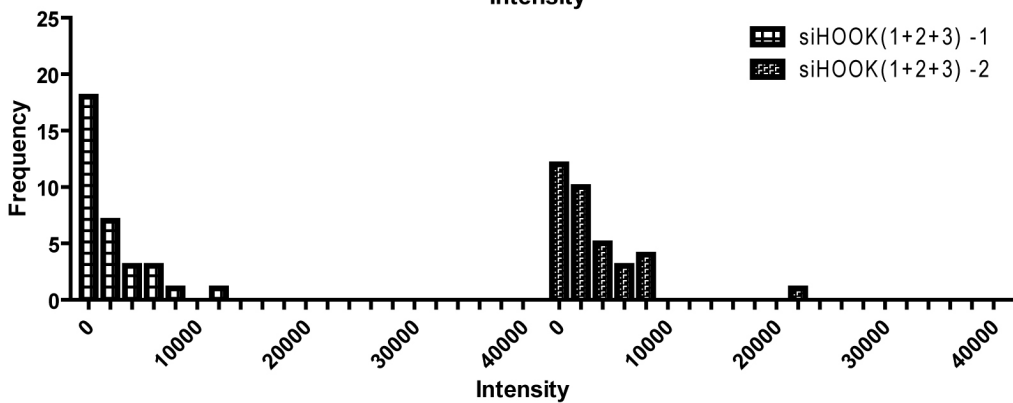
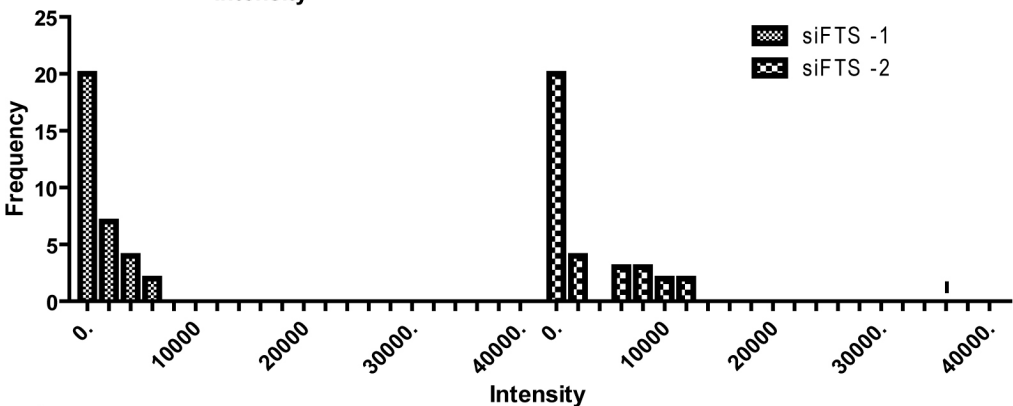
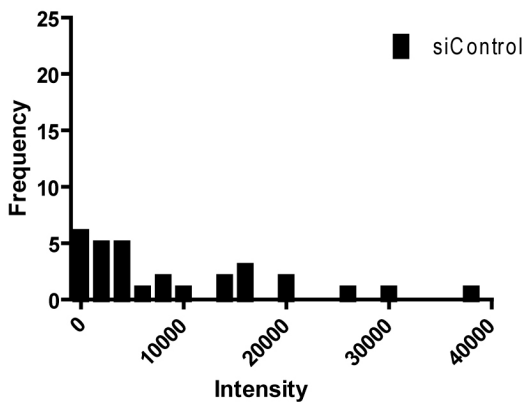
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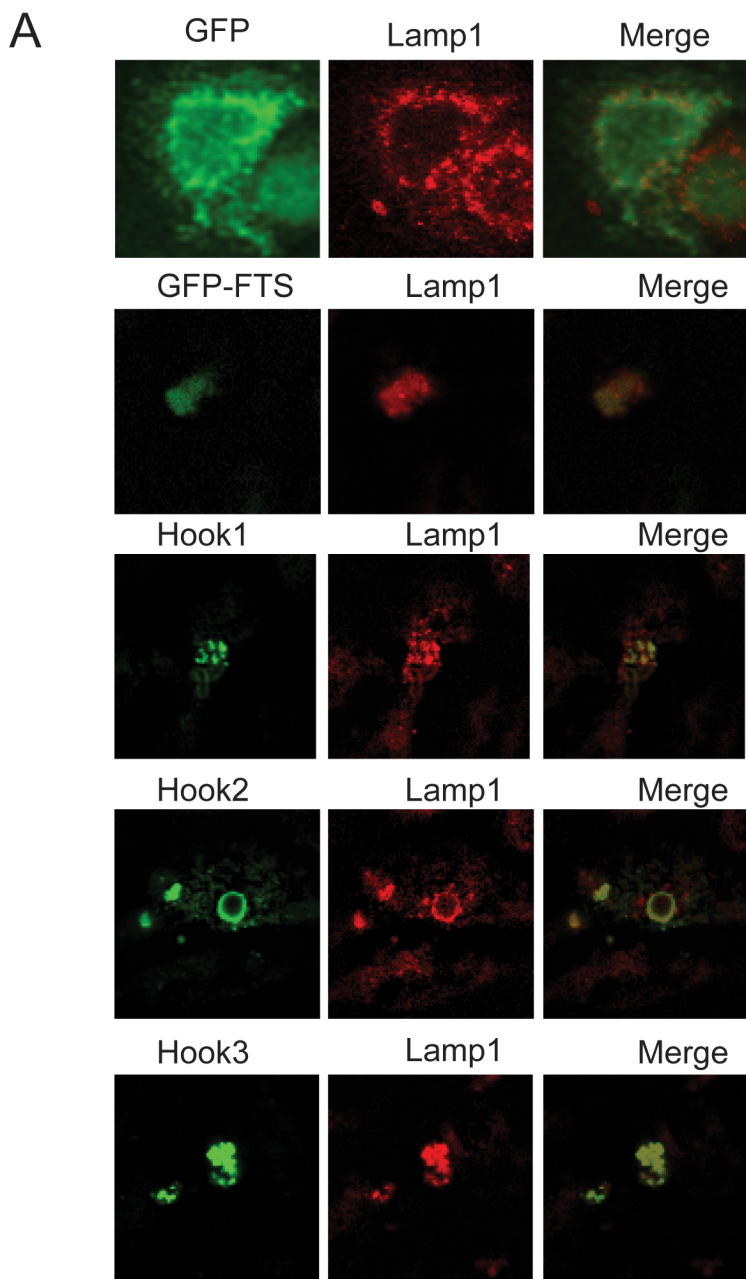
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Figure S3B Analysis of p107FHIP for Coiled-coils

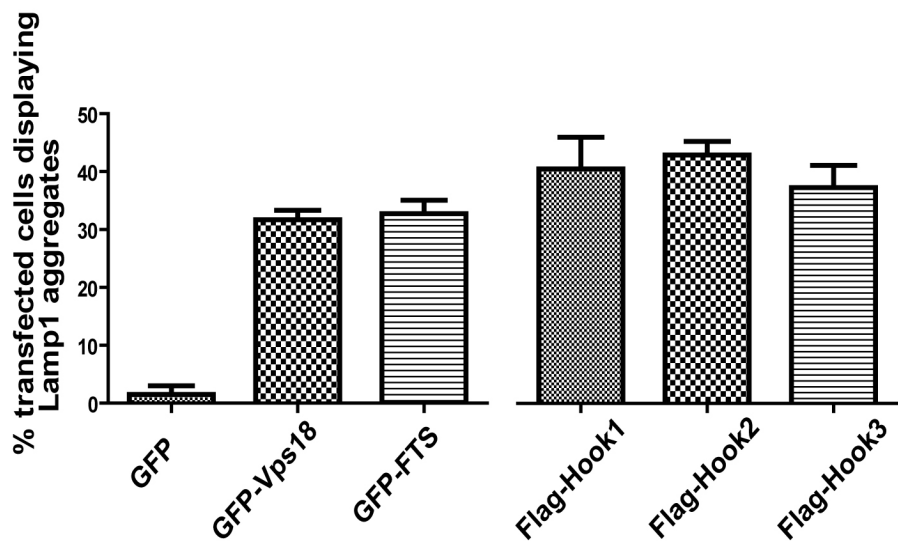


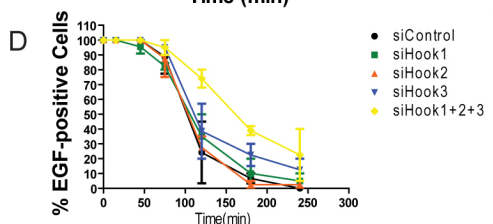
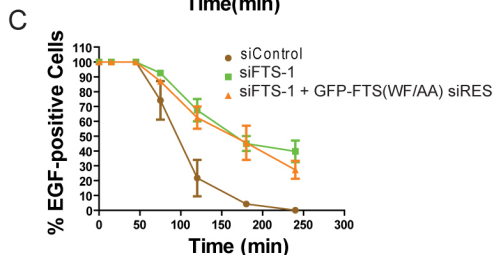
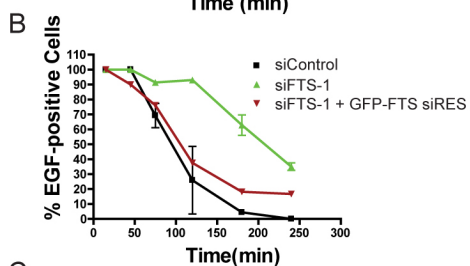
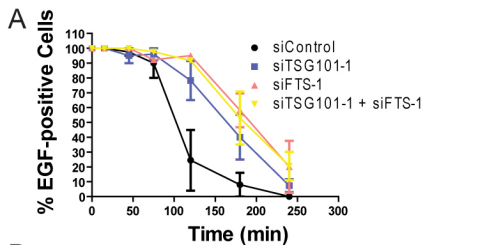






**B**





**E**

siControl

siFTS-1

siFTS-1 + GFP-FTS siRES

