

## Supplementary Material

**Figure S1** Phylogenetic tree of *NIFOXO* and its homologues.

*Aa*, *Aedes aegypti*, ABK76646.1; *Ad*, *Apis dorsata*, XP\_006623461.1; *Af*, *Apis florea*, XP\_003692941.1; *Amel*, *Apis mellifera*, XP\_001122804.2; *Amex*, *Astyanax mexicanus*, XP\_007258711.1; *Ap*, *Acyrtosiphon pisum*, XP\_001944722.2; *Bg*, *Blattella germanica*, CCF23214.1; *Bi*, *Bombus impatiens*, XP\_003487689.1; *Bm*, *Bombyx mori*, AFD99125.1; *Bt*, *Bos Taurus*, NP\_001193012.1; *Ca*, *Chrysochloris asiatica*, XP\_006873780.1; *Cca*, *Ceratitidis capitata*, XP\_004531037.1; *Ccr*, *Condylura cristata*, XP\_004680393.1; *Ce*, *Caenorhabditis elegans*, O16850.3; *Cg*, *Crassostrea gigas*, EKC23646.1; *Ch*, *Clytia hemisphaerica*, ABG21226.1; *Ci*, *Ciona intestinalis*, NP\_001071717.1; *Clf*, *Canis lupus familiaris*, XP\_003639448.1; *Cp*, *Culex pipiens*, AEI86721.1; *Css*, *Ceratotherium simum*, XP\_004443237.1; *Dm*, *Drosophila melanogaster*, NP\_996205.1; *Dr*, *Danio rerio*, NP\_571160.1; *Ee*, *Elephantulus edwardii*, XP\_006879673.1; *Gg*, *Gallus gallus*, XP\_001234496.2; *Gmm*, *Glossina morsitans morsitans*, AFQ01085.1; *Hg*, *Heterocephalus glaber*, XP\_004889213.1; *Hsal*, *Harpegnathos saltator*, EFN84381.1; *Hsap*, *Homo sapiens*, NP\_001446.1; *Lc*, *Latimeria chalumnae*, XP\_005993189.1; *Mb*, *Myotis brandtii*, XP\_005862824.1; *Md*, *Musca domestica*, XP\_005190128.1; *Mmul*, *Macaca mulatta*, XP\_001093593.1; *Mmus*, *Mus musculus*, NP\_062714.1; *Mo*, *Metaseiulus occidentalis*, XP\_003741272.1; *Mr*, *Megachile rotundata*, XP\_003705281.1; *Nl*, *Nilaparvata lugens*, KM250122; *Nv*, *Nasonia vitripennis*, XP\_001607658.2; *Pa*, *Pteropus alecto*, XP\_006909082.1; *Pmb*, *Peromyscus maniculatus bairdii*, XM\_006977605.1; *Pt*, *Pan troglodytes*, XP\_003311562.1; *Rn*, *Rattus norvegicus*, NP\_001099865.1; *Sh*, *Sarcophilus harrisi*, XP\_003769392.1; *Sk*, *Saccoglossus kowalevskii*, NP\_001158440.1; *Sm*, *Schistosoma mansoni*, ABG78546.1; *Sp*, *Strongylocentrotus purpuratus*, ABB89484.1; *Ss*, *Sus scrofa*, NP\_999179.2; *Tca*, *Tribolium castaneum*, XP\_975200.1; *Tch*, *Tupaia chinensis*, XP\_006154300.1; *Tml*, *Trichechus manatus latirostris*, XP\_004388138.1; *Ts*, *Trichinella spiralis*, XP\_003372811.1; *Tt*, *Tursiops truncatus*, XP\_004315811.1; *Xl*, *Xenopus laevis*, ACO24747.1; *Xm*, *Xiphophorus maculatus*, AAK74186.1.

**Figure S2** Phylogenetic tree of *NIAkt* and its homologues.

*Am*, *Alligator mississippiensis*, XM\_006257899.1; *As*, *Alligator sinensis*, XM\_006031384.1; *Ag*, *Anopheles gambiae*, XM\_003435996; *Bas*, *Balaenoptera acutorostrata scammoni*, XM\_007176250.1; *Bm*, *Bos mutus*, XM\_005890586.1; *Bt*, *Bos Taurus*, XM\_005218981.1; *Bb*, *Bubalus bubalis*, XM\_006050047.1; *Cf*, *Camelus ferus*, XM\_006177926.1; *Clf*, *Canis lupus familiaris*, XM\_005623876.1; *Ch*, *Capra hircus*, XM\_005692409.1; *Cl*, *Chinchilla lanigera*, XM\_005410843.1; *Ca*, *Chrysochloris asiatica*, XM\_006839485.1; *Cc*, *Condylura cristata*, XM\_004694120.1; *Cq*, *Culex quinquefasciatus*, XM\_001849205.1; *Dm*, *Drosophila melanogaster*, NM\_169706.2; *Ef*, *Eptesicus fuscus*, XM\_008139592.1; *Ec*, *Equus caballus*, XM\_001492713.4; *Ep*, *Equus przewalskii*, XM\_008506799.1; *Ee*, *Erinaceus europaeus*, XM\_007518365.1; *Fc*, *Felis catus*, XM\_006933187.1; *Ggg*, *Gorilla gorilla gorilla*, XM\_004055779.1; *Hl*, *Haemaphysalis longicornis*, AB601888.1; *Ha*, *Helicoverpa armigera*, N399217.1; *Hs*, *Homo sapiens*, KJ890652.1; *Lo*, *Lepisosteus oculatus*, XM\_006627598.1; *Lw*, *Leptonychotes weddellii*, XM\_006738332.1; *La*, *Loxodonta Africana*, XM\_003408651.1; *Md*, *Musca domestica*, XM\_005186450.1; *Mp*, *Mustela putorius*, XM\_004796606.1; *Mb*, *Myotis brandtii*, XM\_005868806.1; *MI*, *Myotis lucifugus*, XM\_006096753.1; *Nl*, *Nilaparvata lugens*, KM2501

21; *Nle*, *Nomascus leucogenys*, XM\_003276210.2; *Op*, *Ochotona princeps*, XM\_004584261.1; *Or*, *Odobenus rosmarus*, XM\_004395604.1; *Pp*, *Pan paniscus*, XM\_003806999.1; *Pa*, *Pteropus alecto*, XM\_006925608.1; *Sa*, *Sorex araneus*, XM\_004603607.1; *Sp*, *Stegastes partitus*, XM\_008284966.1; *Ss*, *Sus scrofa*, HQ687753.1; *Tml*, *Trichechus manatus latirostris*, XM\_004376758.1.

**Figure S3** Phylogenetic tree of *NPIP3K* and its homologues.

*Ap*, *Anas platyrhynchos*, XM\_005024480.1; *Ad*, *Apis dorsata*, XM\_006623134.1; *Af*, *Apis florea*, XM\_003697036.1; *Am*, *Astyanax mexicanus*, XM\_007228848.1; *Bt*, *Bombus terrestris*, XM\_003392868.1; *Cm*, *Callorhynchus milii*, XM\_007889678.1; *Can*, *Calypte anna*, XM\_008496003.1; *Cm*, *Chelonia mydas*, XM\_007064298.1; *Cla*, *Chinchilla lanigera*, XM\_005406860.1; *Cpb*, *Chrysemys picta belli*, XM\_005278661.2; *Cas*, *Chrysochloris asiatica*, XM\_006846635.1; *Cli*, *Columba livia*, XM\_005505585.1; *Cb*, *Corvus brachyrhynchos*, XM\_008633983.1; *Dm*, *Drosophila melanogaster*, NM\_057785.5; *Et*, *Echinops telfairi*, XM\_004704007.1; *Ef*, *Eptesicus fuscus*, XM\_008153234.1; *Ec*, *Equus caballus*, XM\_001496778.2; *Fc*, *Falco cherrug*, XM\_005445871.1; *Fp*, *Falco peregrinus*, XM\_005242248.1; *Fa*, *Ficedula albicollis*, XM\_005041237.1; *Gg*, *Gallus gallus*, XM\_001235240.2; *Gf*, *Geospiza fortis*, XM\_005423953.1; *Hs*, *Homo sapiens*, NM\_014602.2; *Lo*, *Lepisosteus oculatus*, XM\_006635531.1; *Lv*, *Lipotes vexillifer*, XM\_007462423.1; *La*, *Loxodonta Africana*, XM\_003420917.1; *Mr*, *Megachile rotundata*, XM\_003703820.1; *Mg*, *Meleagris gallopavo*, XM\_003207226.1; *Mu*, *Melopsittacus undulates*, XM\_005141305.1; *Mde*, *Microplitis demolitor*, XM\_008547450.1; *Mdo*, *Monodelphis domestica*, XM\_003342097.2; *Mb*, *Myotis brandtii*, XM\_005863585.1; *Mda*, *Myotis davidii*, XM\_006770215.1; *Ml*, *Myotis lucifugus*, XM\_006083684.1; *Nl*, *Nilaparvata lugens*, KM373311; *Nv*, *Nasonia vitripennis*, XM\_008204184.1; *Op*, *Ochotona princeps*, XM\_004588388.1; *Oaa*, *Orycteropus afer*, XM\_007936842.1; *Og*, *Otolemur garnettii*, XM\_003781713.1; *Pt*, *Pan troglodytes*, XM\_516746.3; *Phc*, *Pediculus humanus corporis*, XM\_002429885.1; *Pc*, *Physeter catodon*, XM\_007115466.1; *Pr*, *Poecilia reticulata*, XM\_008430629.1; *Ph*, *Pseudopodoces humilis*, XM\_005518997.1; *Pb*, *Python bivittatus*, XM\_007433030.1; *St*, *Spermophilus tridecemlineatus*, XM\_005327000.1; *Sp*, *Stegastes partitus*, XM\_008297967.1; *Tg*, *Taeniopygia guttata*, XM\_002198545.1; *Tc*, *Tribolium castaneum*, XM\_965590.2; *Tm*, *Trichechus manatus*, XM\_004381391.1; *Za*, *Zonotrichia albicollis*, XM\_005480995.1.

**Figure S4** Phylogenetic tree of *NIPDK* and its homologues.

*Ap*, *Acyrtosiphon pisum*, XM\_001950984.3; *Ad*, *Apis dorsata*, XM\_006608687.1; *Af*, *Apis florea*, XM\_003697518.1; *Am*, *Apis mellifera*, XM\_006567943.1; *At*, *Arabidopsis thaliana*, AF132742.1; *Bi*, *Bombus impatiens*, XM\_003487039.1; *Bt*, *Bombus terrestris*, XM\_003396474.1; *Dm*, *Drosophila melanogaster*, NM\_080382.4; *Hl*, *Haemaphysalis longicornis*, AB617886.1; *Hb*, *Haplochromis burtoni*, XM\_005939509.1; *Hs*, *Homo sapiens*, AF017995.1; *Le*, *Lycopersicon esculentum*, AY849915.1; *Mz*, *Maylandia zebra*, XM\_004562456.1; *Mr*, *Megachile rotundata*, XM\_003708447.1; *Md*, *Microplitis demolitor*, XM\_008560785.1; *Nb*, *Neolamprologus brichardi*, XM\_006801043.1; *Nl*, *Nilaparvata lugens*, KM373312; *Nv*, *Nasonia vitripennis*, XM\_008204995.1; *On*, *Oreochromis niloticus*, XM\_003438771.2; *Oa*, *Orycteropus afer*, XM\_007939543.1; *Ol*, *Oryzias latipes*, XM\_004080354.1; *Pf*, *Poecilia Formosa*, XM\_007576622.1; *Pr*, *Poecilia reticulata*, XM\_008436325.1; *Pb*, *Python bivittatus*, XM\_007439249.1; *Sp*, *Stegastes partitus*, XM\_008303696.1; *Tr*, *Takifugu rubripes*, XM\_003961305.1; *Xm*, *Xiphophorus maculatus*, XM\_005803239.1.

Figure S5 QRT-PCR measurement of the expression of *NIP13K*, *NIakt*, *NIPDK1* and *NIFOXO* after dsRNA knockdown /double knockdown of *PI3K/Akt/FOXO* Signaling.

Figure S1

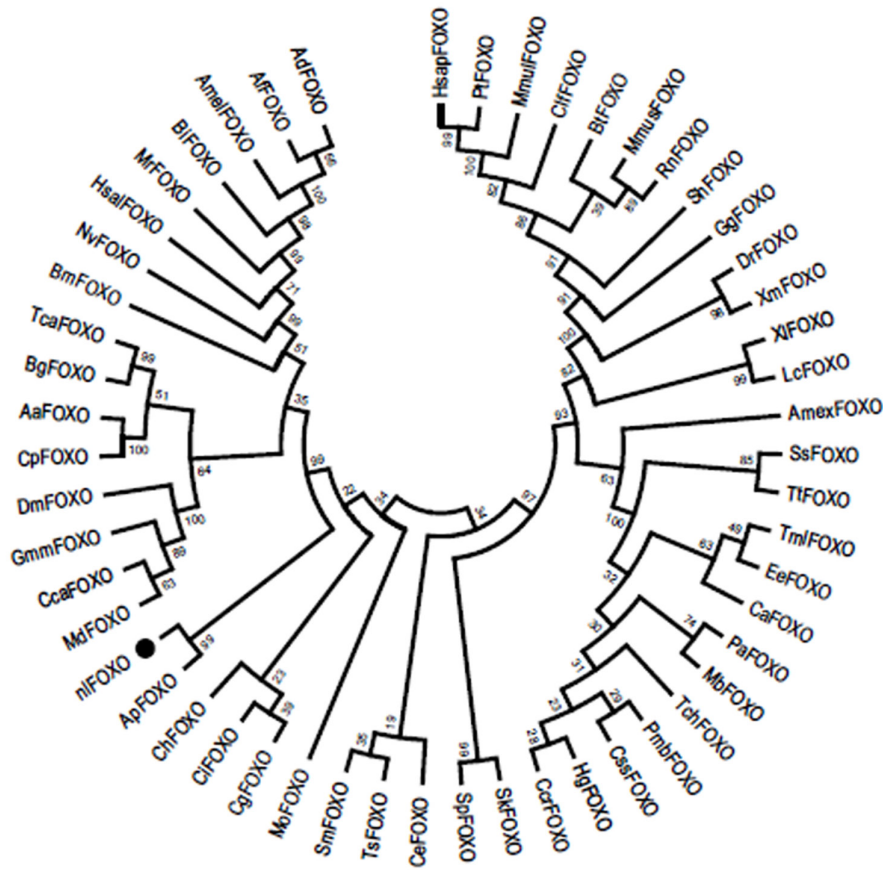


Figure S2

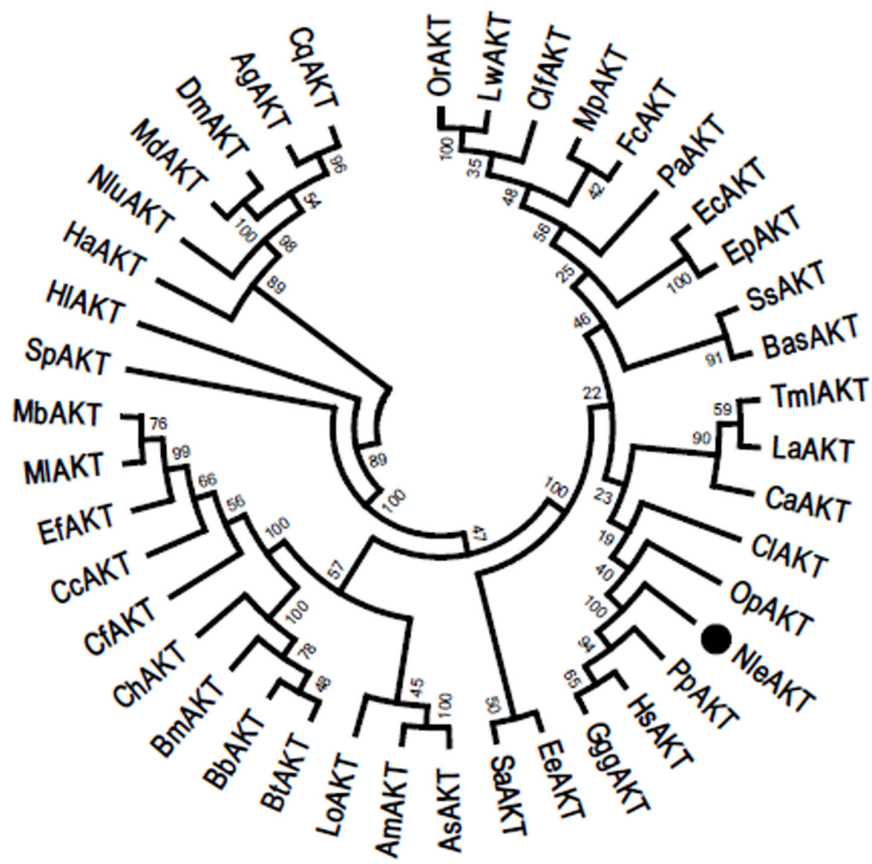


Figure S3

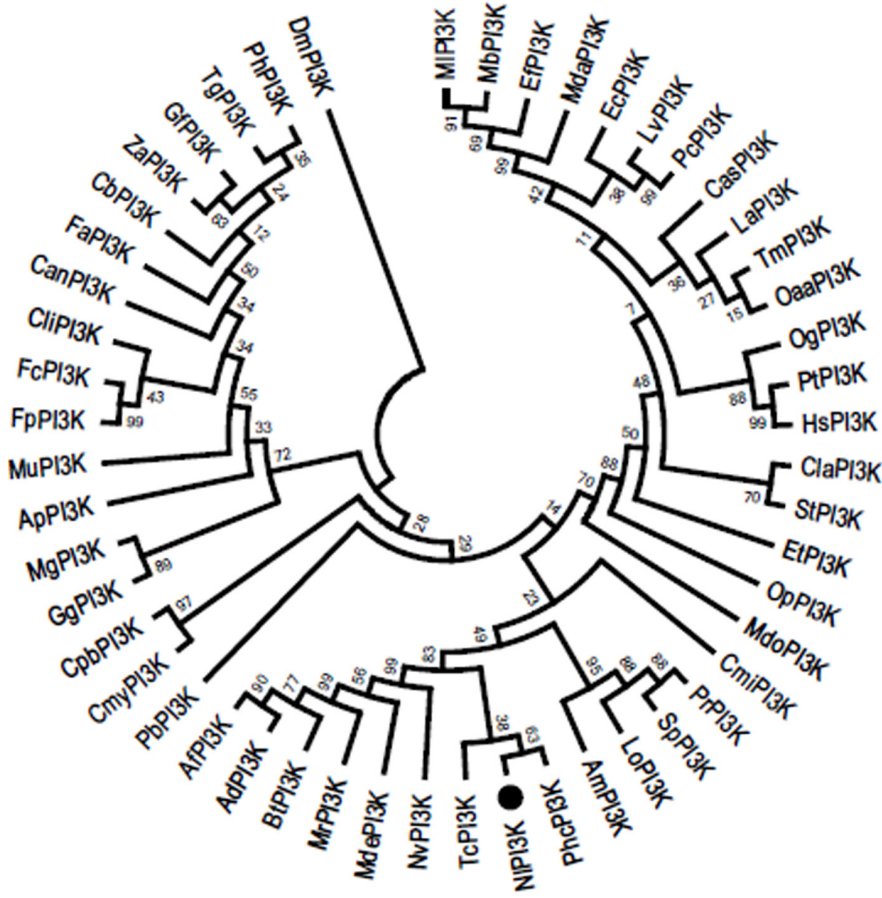


Figure S4

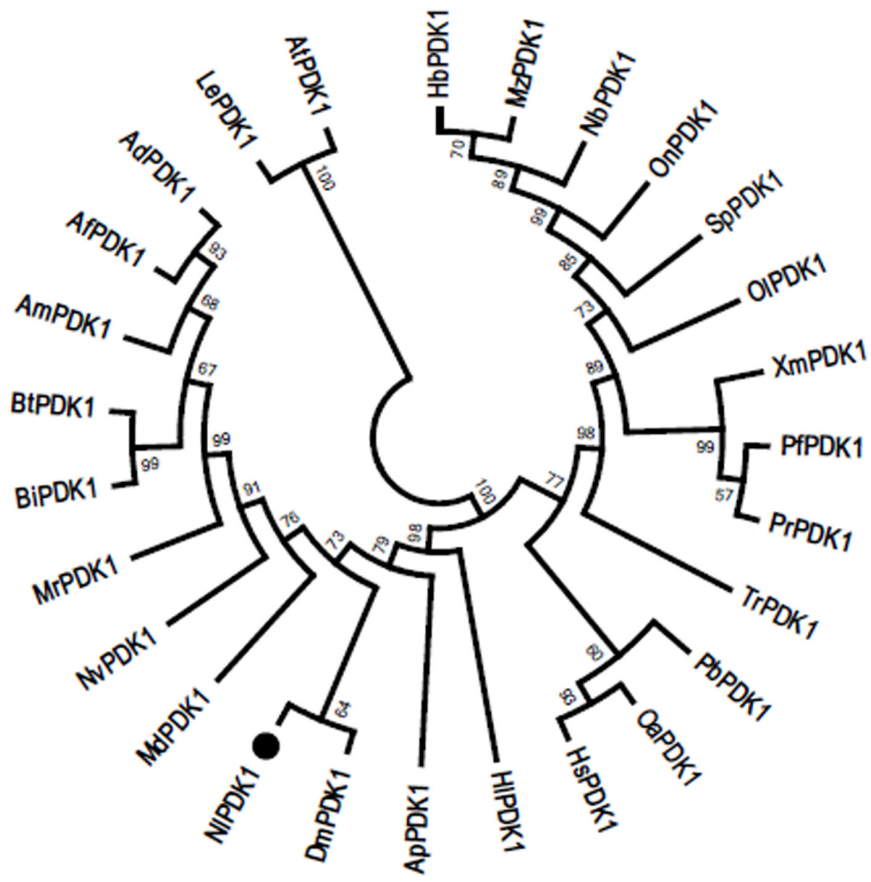
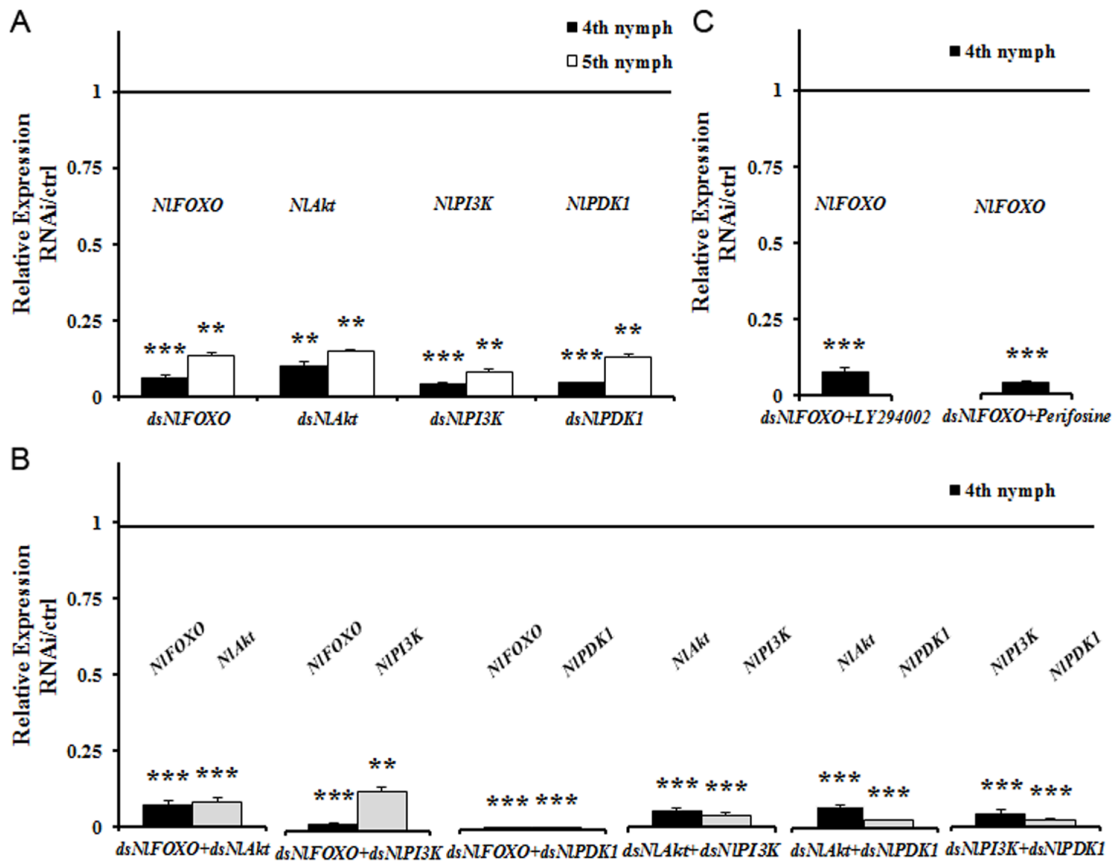


Figure S5



**Table S1** Parameters measured and calculated for cluster analysis.

Catatory	Treatment	Body length (10 <sup>-3</sup> m)	Body weight(10 <sup>-3</sup> g)	Bristle number/wing area(bristle/10 <sup>-6</sup> m <sup>2</sup> )	
<b>SWF</b>	NC	3.25	2.45	144.20	
	dsGFP	3.41	1.80	157.78	
	dsNIAkt	3.16	1.44	160.62	
	dsNIPI3K	3.22	2.41	185.46	
	dsNIPDK1	3.18	1.70	196.99	
	LY294002	3.41	2.14	137.81	
	Perifosine(SWF)	3.36	1.76	172.09	
	dsNIFOXO+dsNIAkt	3.29	1.76	150.01	
	dsNIFOXO+dsNIPI3K	3.06	2.09	193.79	
	dsNIAkt+dsNIPI3K	3.12	2.03	180.16	
	dsNIAkt+dsNIPDK1	3.19	1.79	196.01	
	dsNIPI3K+dsNIPDK1	3.14	1.73	160.86	
	<b>SWM</b>	NC	2.87	1.01	202.80
		dsGFP	2.50	0.93	216.28
dsNIAkt		2.37	0.75	243.33	
dsNIPI3K		2.78	1.36	209.15	
dsNIPDK1		2.39	0.73	246.97	
LY294002		2.50	1.02	211.02	
Perifosine		2.41	1.06	159.80	
dsNIFOXO+dsNIAkt		2.60	1.20	234.37	
dsNIAkt+dsNIPI3K		2.53	1.10	199.94	
dsNIAkt+dsNIPDK1		2.47	0.92	236.72	
dsNIPI3K+dsNIPDK1		2.41	0.93	214.00	
<b>LWF</b>		NC	3.42	2.27	69.78
		dsGFP	3.47	2.17	67.20
		dsNIFOXO	3.55	2.07	75.77
	dsNIPDK1	3.07	1.63	79.03	
	LY294002	3.50	2.70	64.76	
	Perifosine	3.38	2.40	76.73	
	dsNIFOXO+dsNIAkt	3.31	1.78	90.73	
	dsNIFOXO+dsNIPI3K	3.42	2.24	99.36	
	dsNIFOXO+dsNIPDK1	3.34	2.02	93.87	
	dsNIFOXO+LY294002	3.19	2.08	79.38	
	dsNIFOXO+Perifosine	3.16	1.82	98.98	
	<b>LWM</b>	NC	2.99	1.11	78.06
		dsGFP	2.53	1.10	78.44
		dsNIFOXO	2.54	1.02	102.74
dsNIAkt		2.41	1.42	102.25	
dsNIPI3K		2.70	1.08	89.00	
dsNIPDK1		2.50	1.07	81.64	
LY294002	2.56	1.17	71.71		



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Perifosine	2.77	1.57	77.07
dsNIFOXO+dsNIAkt	2.52	0.93	90.49
dsNIFOXO+dsNIP13K	2.59	1.13	91.09
dsNIFOXO+dsNIPDK1	2.54	1.40	78.44
dsNIAkt+dsNIP13K	2.47	1.17	101.56
dsNIAkt+dsNIPDK1	2.47	0.95	84.68
dsNIP13K+dsNIPDK1	2.39	0.98	78.60
dsNIFOXO+LY294002	2.63	1.06	76.12
dsNIFOXO+Perifosine	2.53	0.99	84.32

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