Figure S1. Administration of rCTRP3 mitigates spinal mitochondrial dysfunction in SNI rats. (A-C) Intrathecal rCTRP3 (30 and 90 μg) significantly restored the SNI-induced decreases in mitochondrial membrane potential and ATP production in the spinal cord. ***P<0.001 and ****P<0.0001 vs. sham group; $^{\#\#}$P<0.01 and $^{\#\#\#\#}$P<0.0001 vs. SNI + vehicle group; n=5 rats/group. rCTRP3, recombinant complement C1q tumor necrosis factor-related protein 3; SNI, spared nerve injury; ATP, adenosine triphosphate.

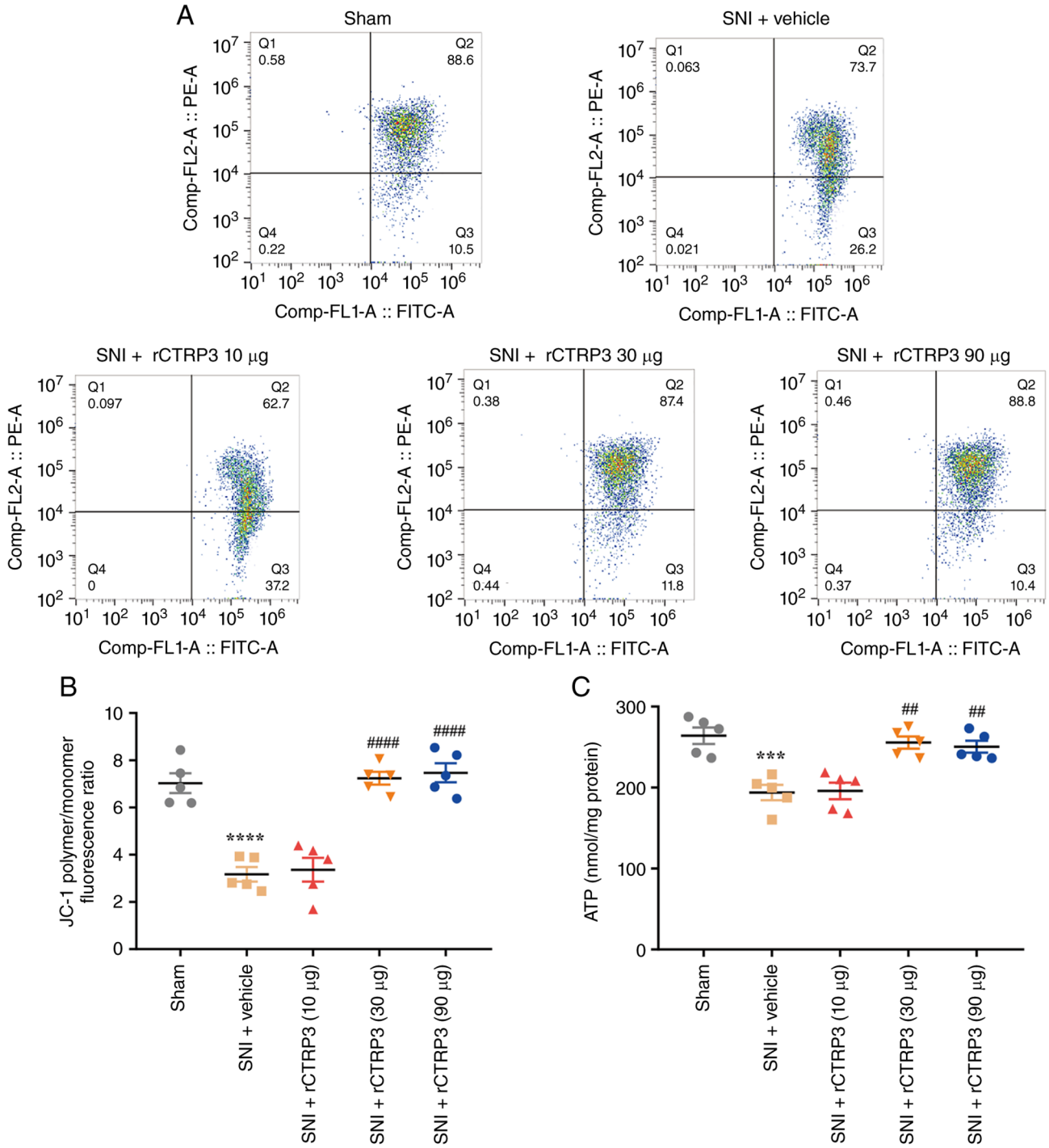

Figure S2. SIRT1 inhibitor abolishes rCTRP3-mediated alleviation of mitochondrial dysfunction in SNI rats. (A-C) The rCTRP3-mediated restoration of mitochondrial membrane potential and ATP production was abolished by the SIRT1 inhibitor EX-527. **P<0.01 and ***P<0.001 vs. sham group; $^{\#\#}$P<0.01 and $^{\#\#\#}$P<0.001 vs. SNI + vehicle group; $^{\&\&}$P<0.01 and $^{\&\&\&}$P<0.001 vs. SNI + rCTRP3 group; n=5 rats/group. SIRT1, sirtuin 1; rCTRP3, recombinant complement C1q tumor necrosis factor-related protein 3; SNI, spared nerve injury; ATP, adenosine triphosphate.

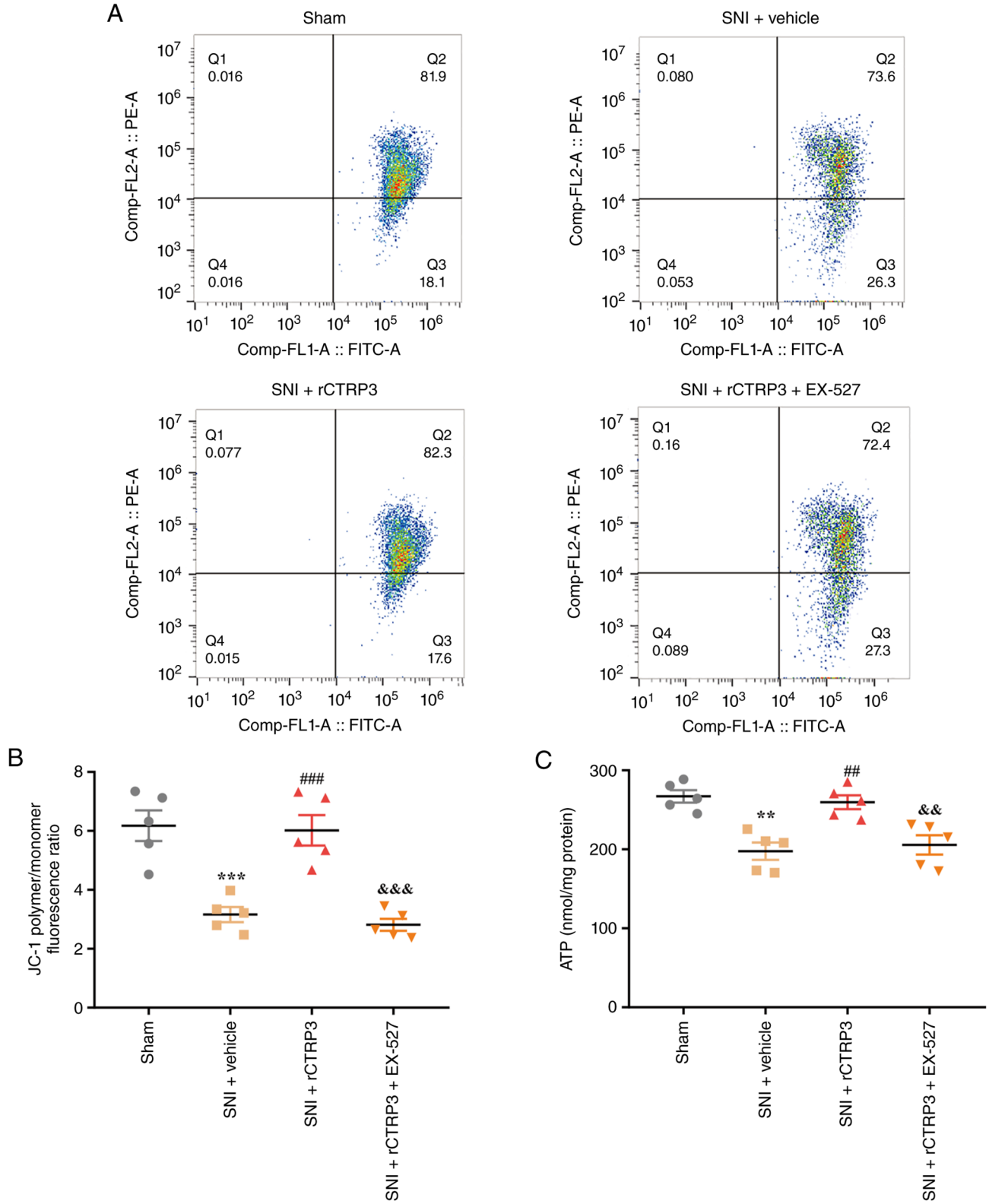

Figure S3. PGC-1α siRNA abolishes rCTRP3-mediated amelioration of ATF5-dependent UPR^{mt} in SNI rats. (A and B) Immunofluorescence staining showed that PGC-1α siRNA significantly blocked rCTRP3-induced upregulation of ATF5 in spinal dorsal horn neurons. (C-F) Consistently, RT-qPCR analysis revealed that PGC-1α silencing completely reversed rCTRP3-mediated enhancement of ATF5, ClpP, Hsp60 and LonP1 mRNA levels in the spinal cord. **P<0.01 and ***P<0.001 vs. sham group; $^{\#\#}$P<0.01 and $^{\#\#\#}$P<0.001 vs. SNI + vehicle group; $^{\&\&}$P<0.01 vs. SNI + rCTRP3 group; n=5 rats/group. PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; siRNA, small interfering RNA; rCTRP3, recombinant complement C1q tumor necrosis factor-related protein 3; ATF5, activating transcription factor 5; UPR^{mt}, mitochondrial unfolded protein response; SNI, spared nerve injury; ClpP, caseinolytic mitochondrial matrix peptidase proteolytic subunit; Hsp60, heat shock protein 60; LonP1, Lon peptidase 1, mitochondrial; RT-qPCR, reverse transcription-quantitative polymerase chain reaction.

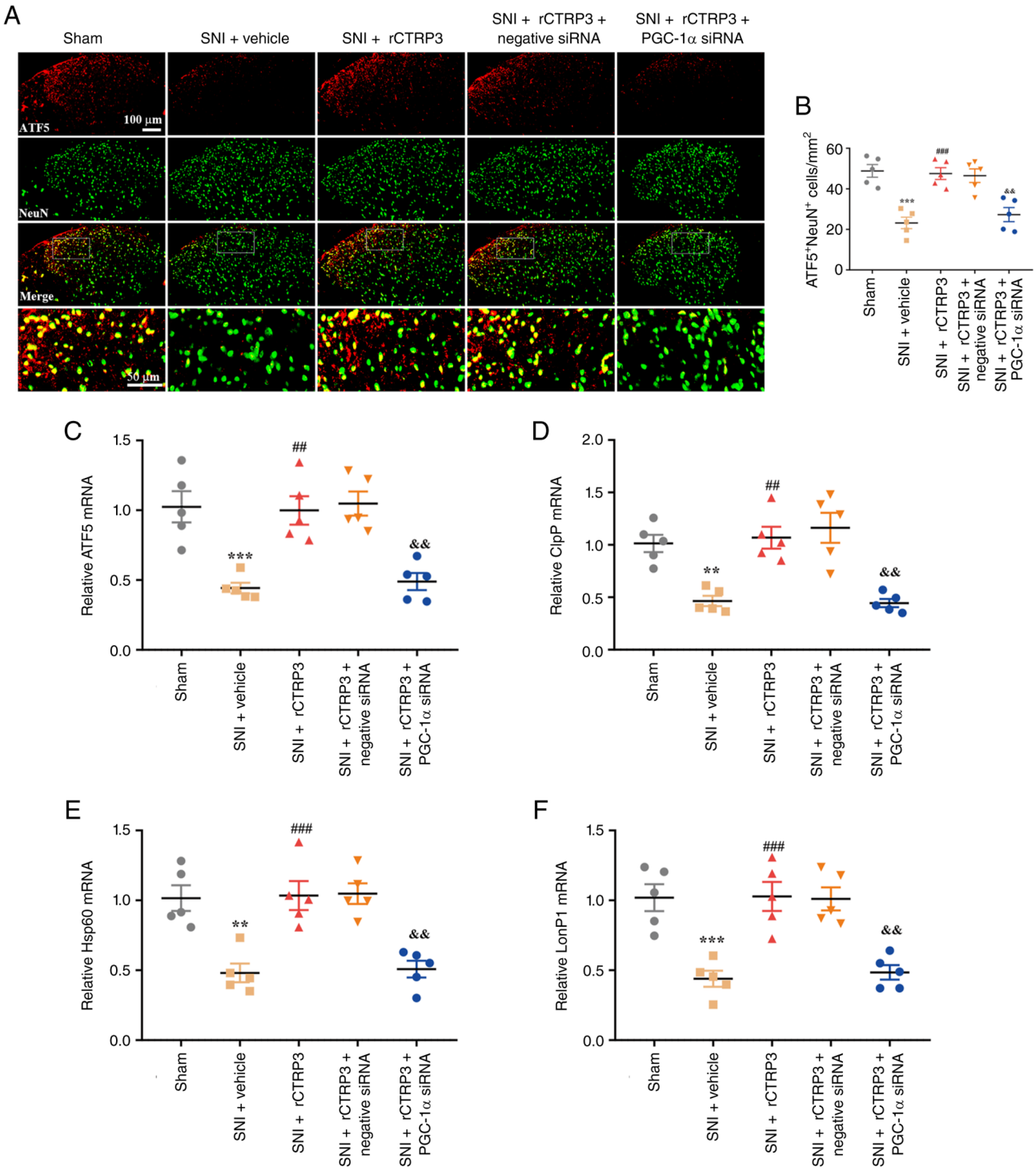

Figure S4. PGC-1α siRNA abolishes rCTRP3-mediated improvement of mitochondrial function in the spinal cord of SNI rats. (A-C) PGC-1α knockdown blunted the rCTRP3-induced recovery of mitochondrial membrane potential and ATP production in the spinal cord following SNI. ***P<0.001 and ****P<0.0001 vs. sham group; $^{\#\#}$P<0.01 and $^{\#\#\#\#}$P<0.0001 vs. SNI + vehicle group; $^{\&\&\&}$P<0.001 vs. SNI + rCTRP3 group; n=5 rats/group. PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; siRNA, small interfering RNA; rCTRP3, recombinant complement C1q tumor necrosis factor-related protein 3; SNI, spared nerve injury; ATP, adenosine triphosphate.

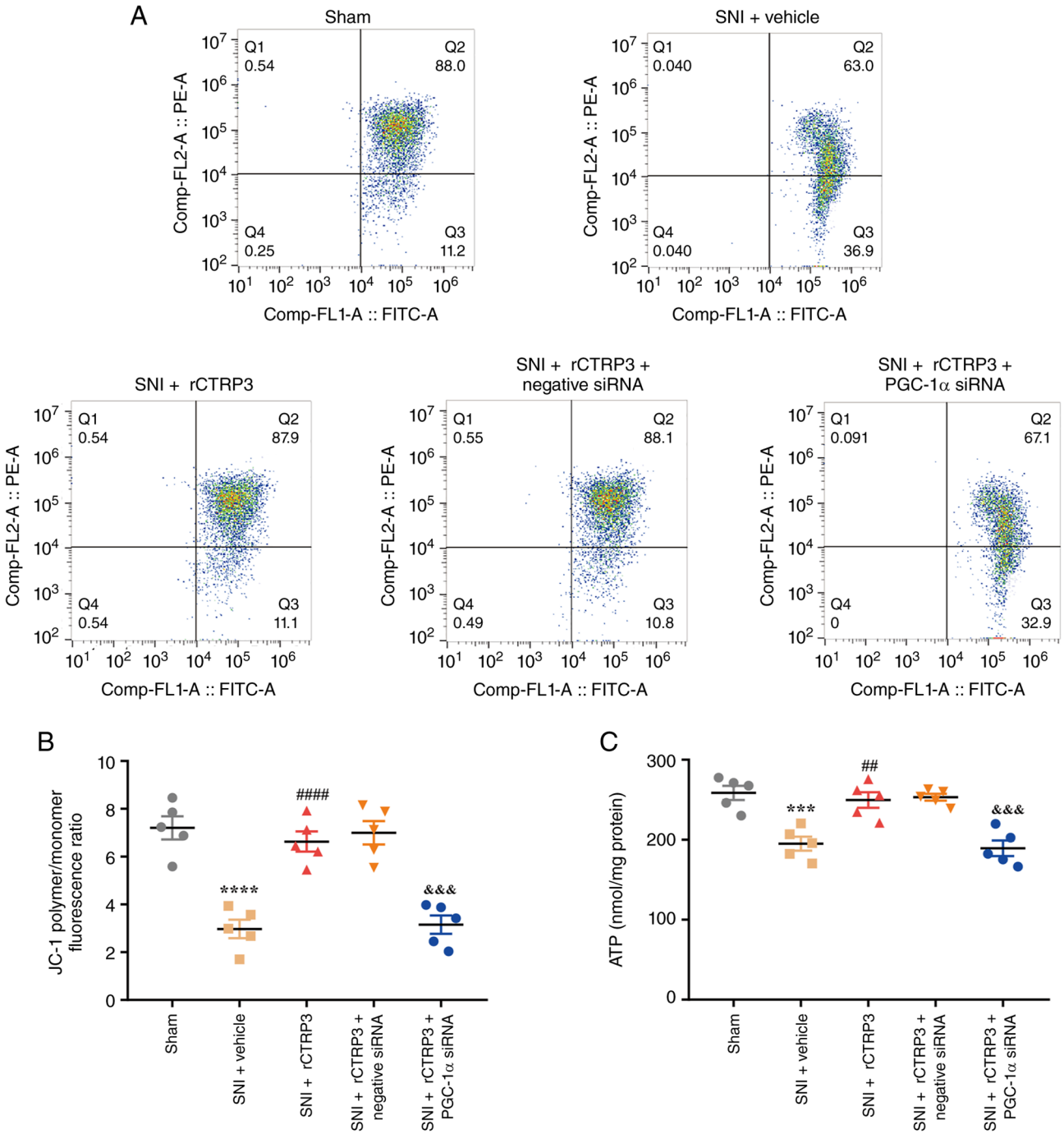

Figure S5. ATF5 siRNA abolishes the rCTRP3-mediated enhancement of PGC-1α-dependent mitochondrial biogenesis in SNI rats. (A and B) Immunofluorescence staining revealed that ATF5 siRNA markedly inhibited the rCTRP3-mediated increase in PGC-1α expression in spinal dorsal horn neurons. (C-E) WB analysis showed that ATF5 silencing significantly reversed the rCTRP3-induced upregulation of PGC-1α, NRF1 and TFAM proteins in the spinal cord. **P<0.01 and ***P<0.001 vs. sham group; $^{\#\#}$P<0.01 and $^{\#\#\#}$P<0.001 vs. SNI + vehicle group; $^{\&\&}$P<0.01 and $^{\&\&\&}$P<0.001 vs. SNI + rCTRP3 group; n=5 rats/group. Abbreviations: ATF5, activating transcription factor 5; siRNA, small interfering RNA; rCTRP3, recombinant complement C1q tumor necrosis factor-related protein 3; SNI, spared nerve injury; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; NRF1, nuclear respiratory factor 1; TFAM, mitochondrial transcription factor A; WB, western blotting.

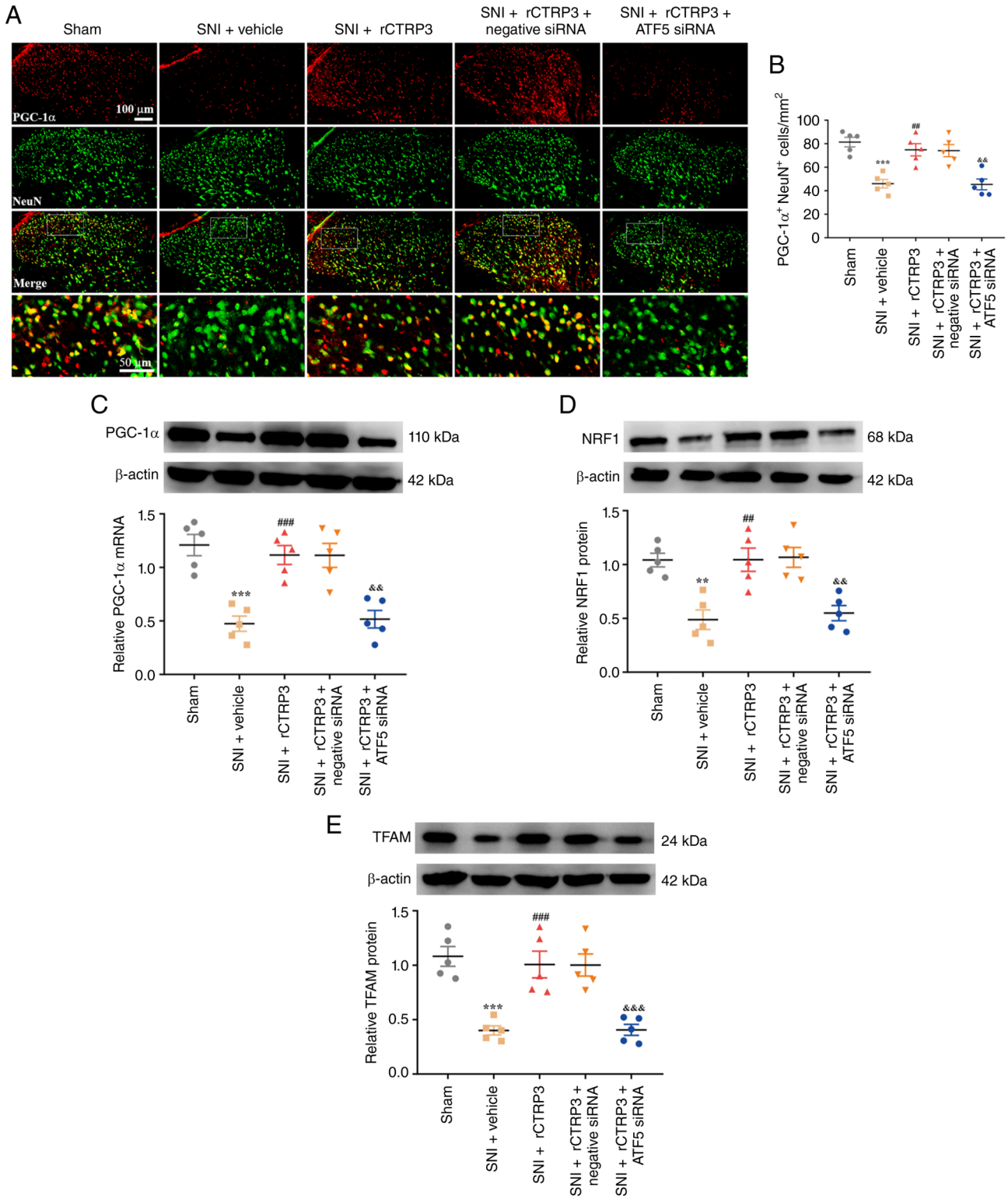

Figure S6. ATF5 siRNA blocks the rCTRP3-mediated recovery of mitochondrial function in SNI rats. (A-C) ATF5 siRNA abolished the rCTRP3-induced recovery of mitochondrial membrane potential and ATP production, indicating that the ATF5-dependent UPR^{mt} is essential for the mitochondrial bioenergetic improvement conferred by rCTRP3. ***P<0.001 vs. sham group; $^{\#\#}$P<0.01 vs. SNI + vehicle group; $^{\&\&}$P<0.01 vs. SNI + rCTRP3 group; n=5 rats/group. ATF5, activating transcription factor 5; siRNA, small interfering RNA; rCTRP3, recombinant complement C1q tumor necrosis factor-related protein 3; SNI, spared nerve injury; ATP, adenosine triphosphate; UPR^{mt}, mitochondrial unfolded protein response.