

Supporting Information

Ternary supramolecular nanocomplexes for superior anticancer efficacy of natural medicine

Supplementary Figure S1. Primary physiochemical properties of E@TSN. (a) Size and (b) zeta potential of E@TSN. *In vitro* release file of E@TSN in (c) pH 1.2 0.1 mol/L HCl solution medium and (d) pH 7.8 PBS release medium in 72 h (n=3).

Supplementary Figure S2. Proliferation of SCLC H446 cells when treated with BSN, EA and E@TSN (equivalent to 10 μ M EA) for (a) 48 h and (b) 72 h.

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Supplementary Table S12. Gene ontology enrichment between BSN group and Control group (component ontology) ($P < 0.05$).

Supplementary Table S13. Gene ontology enrichment between BSN group and Control group (function ontology) ($P < 0.05$).

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Supplementary Table S15. Kyoto encyclopedia of genes and genomes enrichment between E@TSN group and Control group ($P < 0.05$).

Supplementary Table S16. Kyoto encyclopedia of genes and genomes enrichment

between EA group and Control group ($P<0.05$).

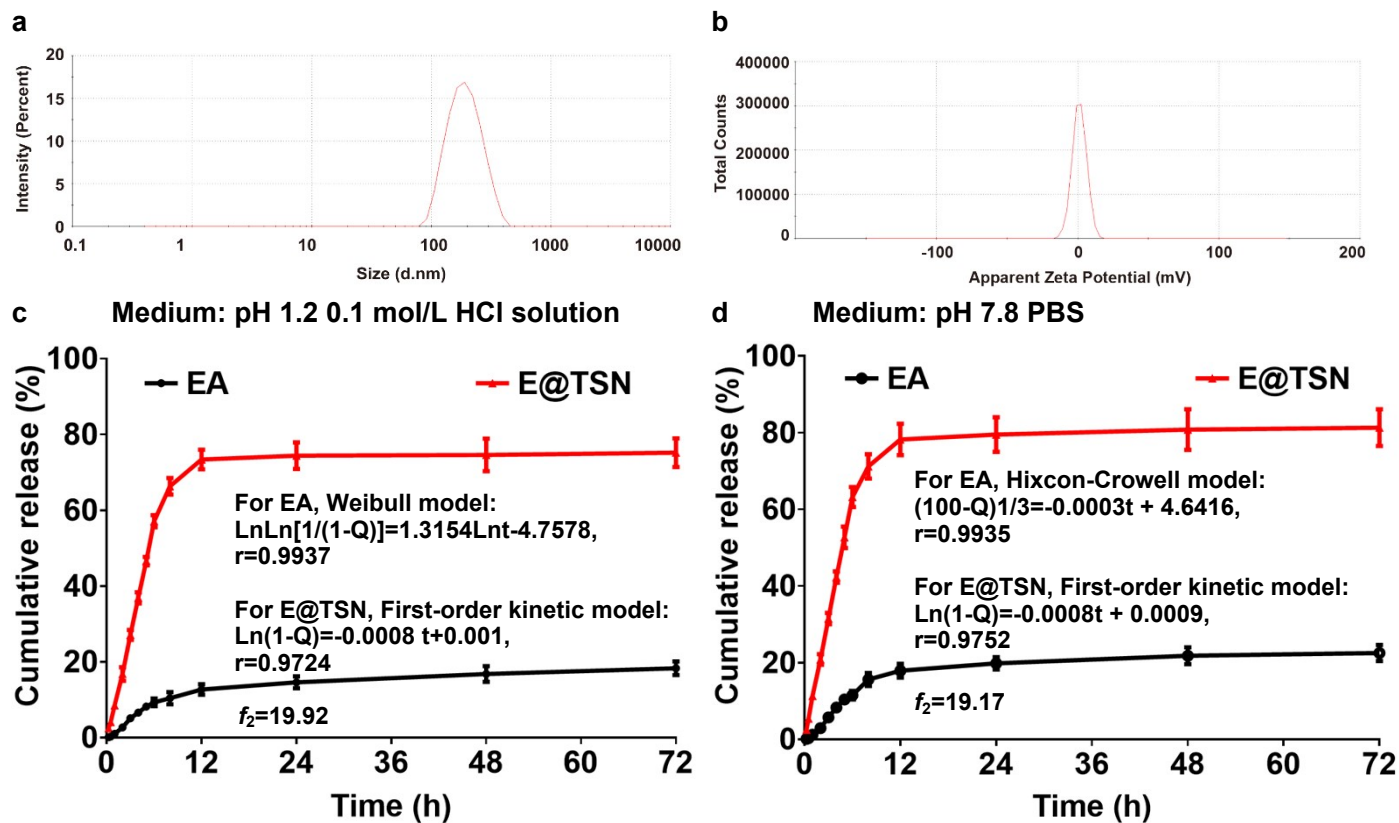
Supplementary Table S17. Kyoto encyclopedia of genes and genomes enrichment between BSN group and Control group ($P<0.05$).

Supplementary Table S18. Blood index of mice in Control group, BSN group, EA group and E@TSN group.

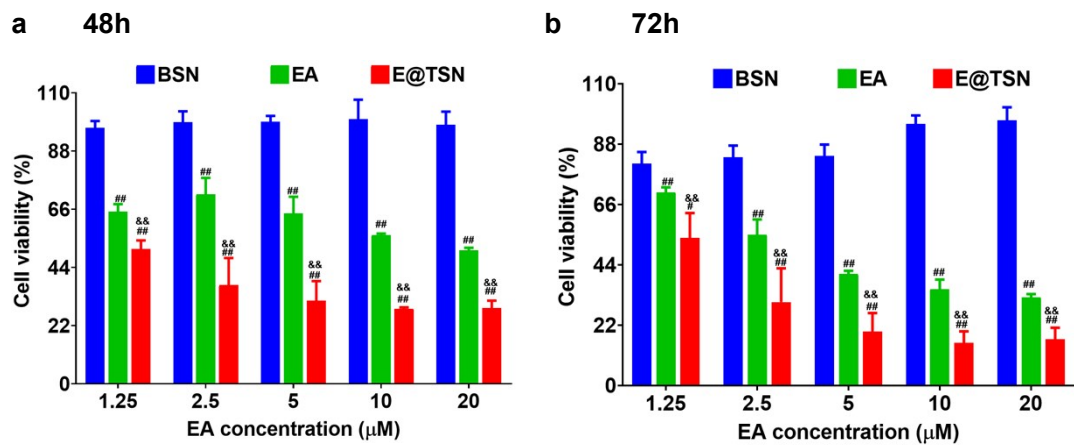
Supplementary Table S19. Biochemical indicator of mice in Control group, BSN group, EA group and E@TSN group.

Supplementary Methods

Solubility and oil-water partition coefficient assay.



Supplementary Figure S1. Primary physiochemical properties of E@TSN. (a) Size and (b) zeta potential of E@TSN. *In vitro* release file of E@TSN in (c) pH 1.2 0.1 mol/L HCl solution medium and (d) pH 7.8 PBS release medium in 72 h (n=3).



Supplementary Figure S2. Proliferation of SCLC H446 cells when treated with BSN, EA and E@TSN (equivalent to 10 μM EA) for (a) 48 h and (b) 72 h.

Supplementary Table S1. Coded levels and “real” values for each factor under study.

| Factors | Levels | | | | |
|---------------------|--------|------|------|------|-------|
| | -1.732 | -1 | 0 | 1 | 1.732 |
| X1 (EA, mol) | 1 | 1.85 | 3 | 4.15 | 5 |
| X2 (PL/EA, mol:mol) | 0.5 | 1.03 | 1.75 | 2.47 | 3 |
| X3 (HCD/PL mol:mol) | 0.5 | 0.93 | 1.5 | 2.07 | 2.5 |

| Supplementary Table S2. Results of orthogonal design (n = 3). | | | | | |
|----------------------------------------------------------------------|-----------------|------------------------|-------------------------|----------------------------------|-------------------------------|
| Batches | X1 (EA, mol) | X2 (PL/EA, mol:mol) | X3 (HCD/PL, mol:mol) | Experimental complex rate (%) | Estimated complex rate (%) |
| 1 | 4.15 | 2.47 | 0.93 | 27.82 ± 1.78 | 33.18 |
| 2 | 4.15 | 2.47 | 2.07 | 31.51 ± 3.64 | 34.93 |
| 3 | 4.15 | 1.03 | 0.93 | 32.22 ± 0.89 | 29.45 |
| 4 | 1.01 | 1.75 | 1.50 | 75.36 ± 0.97 | 86.86 |
| 5 | 3.00 | 1.75 | 2.49 | 53.35 ± 0.47 | 53.74 |
| 6 | 3.00 | 0.50 | 1.50 | 47.28 ± 1.66 | 48.98 |
| 7 | 1.85 | 2.47 | 0.93 | 85.25 ± 0.75 | 73.23 |
| 8 | 4.15 | 1.03 | 2.07 | 28.23 ± 0.70 | 31.21 |
| 9 | 1.85 | 1.03 | 0.93 | 83.44 ± 1.03 | 69.50 |
| 10 | 1.85 | 2.47 | 2.07 | 85.80 ± 0.63 | 74.98 |
| 11 | 3.00 | 1.75 | 0.51 | 40.40 ± 3.38 | 50.69 |
| 12 | 1.85 | 1.03 | 2.07 | 73.00 ± 2.51 | 71.25 |
| 13 | 3.00 | 3.00 | 1.50 | 54.57 ± 2.16 | 55.45 |
| 14 | 4.99 | 1.75 | 1.50 | 33.53 ± 0.72 | 17.57 |
| 15-20 | 3.00 | 1.75 | 1.50 | 48.76 ± 1.61 | 52.22 |

Supplementary Table S3. Primer sets for PCR were listed.

| Gene | Primer sequences | Amplification size (bp) | Annealing temperature (°C) |
|-------|----------------------------------------------------------------------------------------|-------------------------|----------------------------|
| CD133 | Forward: 5¢-TTGCAACAACATCAGAATGTCT-3¢ Reverse: 5¢-ACATCAAGCCCAGGTAATAAAA -3¢ | 428 | 61 |
| CD44 | Forward: 5¢-TATTTGTGCTGCAAACCATACA -3¢ Reverse: 5¢-CACATCCAATTATTTTGCTCCT -3¢ | 401 | 55 |
| ABCG2 | Forward: 5¢-GTTGTGATGGGCACTCTGAC-3¢ Reverse: 5¢-CCCTGTTAATCCGTTTCGTTT-3¢ | 106 | 55 |

| Supplementary Table S4. Mathematical models of mean cumulative release rate versus time of E@TSN and EA. | | | | | | | | |
|----------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|--------------------------------------------------------------|------------------------------------------------------------|--------------------------------------------------------------|--------------------------------------------------------------|--------------------------------------------------------------|--------------------------------------------------------------|--------------------------------------------------------------|
| Model | E@TSN | | | | EA | | | |
| | 0.1 mol/L HCl | pH 6.8 PBS | pH 7.4 PBS | pH 7.8 PBS | 0.1 mol/L HCl | pH 6.8 PBS | pH 7.4 PBS | pH 7.8 PBS |
| Zero-order kinetic | Q=0.0779t -0.0994, r=0.9723 | Q=0.0914t -0.0649, r=0.9775 | Q=0.0887t -0.0872, r=0.9815 | Q=0.0823t -0.0858, r=0.9751 | Q=0.0126t +0.0052, r=0.9834 | Q=0.0233t -0.0017, r=0.9905 | Q=0.0213t -0.0051, r=0.9923 | Q=0.0179t+ 0.0009, r=0.9904 |
| First-order kinetic | Ln(1-Q)= -0.0008t +0.001, r=0.9724 | Ln(1-Q)= -0.0009t +0.0007, r=0.9777 | Ln(1-Q)= -0.0009t +0.0009, r=0.9816 | Ln(1-Q)= -0.0008t+ 0.0009, r=0.9752 | Ln(1-Q)= -0.0136t- 0.0041, r=0.9854 | Ln(1-Q)= -0.0268t 0.0069, r=0.9928 | Ln(1-Q)= -0.0241t +0.0095, r=0.9920 | Ln(1-Q)= -0.0199t+ 0.0018, r=0.9915 |
| Higuchi | Q=0.209t ^{1/2} -0.0529, r=0.8623 | Q=0.2453t ^{1/2} -0.0105, r=0.8723 | Q=0.2386t ^{1/2} -0.0355, r=0.8794 | Q=0.2211t ^{1/2} -0.0368, r=0.8702 | Q=0.0509t ^{1/2} -0.0349, r=0.9879 | Q=0.0924t ^{1/2} -0.0727, r=0.9854 | Q=0.0838t ^{1/2} -0.0688, r=0.9780 | Q=0.0715t ^{1/2} -0.0545, r=0.9888 |
| Hixcon-Crowell | (100-Q) ^{1/3} = -0.0002t +6.6379, r=0.7924 | (100-Q) ^{1/3} = -0.0006t +4.6373, r=0.8094 | (100-Q) ^{1/3} = -6E-6t +4.6416, r=0.8188 | (100-Q) ^{1/3} = -0.0006t +4.6382, r=0.8115 | (100-Q) ^{1/3} = -0.0002t +4.6415, r=0.9835 | (100-Q) ^{1/3} = -0.0004t +4.6416, r=0.9928 | (100-Q) ^{1/3} = -0.0003t +4.6417, r=0.9923 | (100-Q) ^{1/3} = -0.0003t +4.6416, r=0.9935 |
| Ritger-peppas | Q=0.6268t -2.5739, r=0.9365 | Q=0.8133t -2.0015, r=0.9296 | Q=0.8318t -2.1232, r=0.9945 | Q=0.837t -2.2239, r=0.9491 | LnQ=1.2955 Lnt-4.771, r=0.9867 | LnQ=1.4504 Lnt-4.5511, r=0.9884 | LnQ=1.4222 Lnt-4.6481, r=0.9924 | LnQ=1.3884 Lnt-4.6764, r=0.9901 |
| Weibull | LnLn[1/(1- Q)]=0.8648 Lnt-6.9928, r=0.9540 | LnLn[1/(1- Q)]=0.8145 Lnt-6.6055, r=0.9298 | LnLn[1/(1- Q)]=0.8329 Lnt-6.7273, r=0.9454 | LnLn[1/(1- Q)]=0.8381 Lnt-6.8281, r=0.9491 | LnLn[1/(1- Q)]=1.3154 Lnt-4.7578, r=0.9937 | LnLn[1/(1- Q)]=1.4875 Lnt-4.5309, r=0.9954 | LnLn[1/(1- Q)]=1.4552 Lnt-4.6311, r=0.9937 | LnLn[1/(1- Q)]=1.4166 Lnt-4.6101, r=0.9904 |

Supplementary Table S5. Similarity factor (f_2) values of E@TSN and EA in four release media.

| Release profile 1 | | Release profile 2 | | f_2 | Difference |
|-------------------|---------------------|-------------------|---------------------|-------|------------|
| Formulation | Release medium | Formulation | Release medium | | |
| E@TSN | pH 1.2 HCl solution | EA | pH 1.2 HCl solution | 19.92 | Yes |
| E@TSN | pH 6.8 PBS | EA | pH 6.8 PBS | 17.68 | Yes |
| E@TSN | pH 7.8 PBS | EA | pH 7.8 PBS | 19.17 | Yes |
| E@TSN | pH 7.4 PBS | EA | pH 7.4 PBS | 16.54 | Yes |
| E@TSN | pH 1.2 HCl solution | E@TSN | pH 6.8 PBS | 43.66 | Yes |
| E@TSN | pH 1.2 HCl solution | E@TSN | pH 7.8 PBS | 66.08 | No |
| E@TSN | pH 1.2 HCl solution | E@TSN | pH 7.4 PBS | 51.83 | No |
| E@TSN | pH 6.8 PBS | E@TSN | pH 7.8 PBS | 53.00 | No |
| E@TSN | pH 6.8 PBS | E@TSN | pH 7.4 PBS | 67.00 | No |
| E@TSN | pH 7.8 PBS | E@TSN | pH 7.4 PBS | 59.99 | No |
| EA | pH 1.2 HCl solution | EA | pH 6.8 PBS | 60.91 | No |
| EA | pH 1.2 HCl solution | EA | pH 7.8 PBS | 75.49 | No |
| EA | pH 1.2 HCl solution | EA | pH 7.4 PBS | 66.42 | No |
| EA | pH 6.8 PBS | EA | pH 7.8 PBS | 74.51 | No |
| EA | pH 6.8 PBS | EA | pH 7.4 PBS | 86.57 | No |
| EA | pH 7.8 PBS | EA | pH 7.4 PBS | 85.11 | No |

Supplementary Table S6. Gene ontology enrichment between E@TSN group and control group (component ontology) ($P < 0.05$).

| Gene ontology term | Cluster frequency | Protein frequency of use | <i>P</i> value |
|----------------------------------------------|----------------------|--------------------------|----------------|
| Membrane-enclosed lumen | 97/187 genes, 51.9% | 1342/3725 genes, 36.0% | 4.02E-06 |
| Chaperonin-containing T-complex | 5/187 genes, 2.7% | 7/3725 genes, 0.2% | 5.85E-06 |
| Ribonucleoprotein complex | 38/187 genes, 20.3% | 369/3725 genes, 9.9% | 8.32E-06 |
| Organelle lumen | 94/187 genes, 50.3% | 1310/3725 genes, 35.2% | 9.81E-06 |
| Intracellular organelle lumen | 93/187 genes, 49.7% | 1300/3725 genes, 34.9% | 1.34E-05 |
| Non-membrane-bounded organelle | 91/187 genes, 48.7% | 1324/3725 genes, 35.5% | 1.07E-04 |
| Intracellular non-membrane-bounded organelle | 91/187 genes, 48.7% | 1324/3725 genes, 35.5% | 1.07E-04 |
| Nuclear lumen | 75/187 genes, 40.1% | 1041/3725 genes, 27.9% | 1.55E-04 |
| Melanosome | 11/187 genes, 5.9% | 64/3725 genes, 1.7% | 2.73E-04 |
| Pigment granule | 11/187 genes, 5.9% | 64/3725 genes, 1.7% | 2.73E-04 |
| Nuclear periphery | 9/187 genes, 4.8% | 46/3725 genes, 1.2% | 3.66E-04 |
| Nucleus | 110/187 genes, 58.8% | 1736/3725 genes, 46.6% | 3.90E-04 |
| Nuclear chromosome | 14/187 genes, 7.5% | 101/3725 genes, 2.7% | 4.29E-04 |
| Nuclear part | 81/187 genes, 43.3% | 1186/3725 genes, 31.8% | 4.77E-04 |
| Cytosolic part | 14/187 genes, 7.5% | 103/3725 genes, 2.8% | 5.27E-04 |
| Macromolecular complex | 99/187 genes, 52.9% | 1533/3725 genes, 41.2% | 5.60E-04 |
| Nucleolus | 49/187 genes, 26.2% | 639/3725 genes, 17.2% | 9.17E-04 |
| Nuclear lamina | 4/187 genes, 2.1% | 10/3725 genes, 0.3% | 1.02E-03 |
| Catalytic step 2 spliceosome | 11/187 genes, 5.9% | 75/3725 genes, 2.0% | 1.11E-03 |
| Lamin filament | 3/187 genes, 1.6% | 5/3725 genes, 0.1% | 1.16E-03 |
| Extracellular organelle | 3/187 genes, 1.6% | 5/3725 genes, 0.1% | 1.16E-03 |
| Extracellular membrane-bounded organelle | 3/187 genes, 1.6% | 5/3725 genes, 0.1% | 1.16E-03 |
| Extracellular vesicular exosome | 3/187 genes, 1.6% | 5/3725 genes, 0.1% | 1.16E-03 |
| Small ribosomal subunit | 8/187 genes, 4.3% | 44/3725 genes, 1.2% | 1.29E-03 |
| Nucleoplasm | 46/187 genes, 24.6% | 604/3725 genes, 16.2% | 1.60E-03 |
| Organelle inner membrane | 22/187 genes, 11.8% | 229/3725 genes, 6.1% | 2.10E-03 |
| Fibrillar center | 2/187 genes, 1.1% | 2/3725 genes, 0.1% | 2.51E-03 |
| Ku70:Ku80 complex | 2/187 genes, 1.1% | 2/3725 genes, 0.1% | 2.51E-03 |
| Microtubule | 13/187 genes, 7.0% | 109/3725 genes, 2.9% | 2.82E-03 |
| Chromosome | 22/187 genes, 11.8% | 235/3725 genes, 6.3% | 2.92E-03 |

| | | | |
|----------------------------------------------------|----------------------|------------------------|----------|
| Spliceosomal complex | 13/187 genes, 7.0% | 111/3725 genes, 3.0% | 3.31E-03 |
| Cell surface | 11/187 genes, 5.9% | 86/3725 genes, 2.3% | 3.41E-03 |
| Cytosolic small ribosomal subunit | 6/187 genes, 3.2% | 32/3725 genes, 0.9% | 4.48E-03 |
| Eukaryotic translation initiation factor 3 complex | 4/187 genes, 2.1% | 15/3725 genes, 0.4% | 5.43E-03 |
| Cytosolic ribosome | 8/187 genes, 4.3% | 55/3725 genes, 1.5% | 5.54E-03 |
| Chromosomal part | 19/187 genes, 10.2% | 203/3725 genes, 5.4% | 5.64E-03 |
| MCM complex | 3/187 genes, 1.6% | 8/3725 genes, 0.2% | 5.78E-03 |
| Ribosomal subunit | 10/187 genes, 5.3% | 81/3725 genes, 2.2% | 6.68E-03 |
| Polysome | 4/187 genes, 2.1% | 16/3725 genes, 0.4% | 6.95E-03 |
| Mitochondrial crista | 2/187 genes, 1.1% | 3/3725 genes, 0.1% | 7.27E-03 |
| Nuclear chromosome part | 10/187 genes, 5.3% | 83/3725 genes, 2.2% | 7.93E-03 |
| Organelle part | 135/187 genes, 72.2% | 2377/3725 genes, 63.8% | 8.08E-03 |
| Intermediate filament cytoskeleton | 6/187 genes, 3.2% | 36/3725 genes, 1.0% | 8.16E-03 |
| Mitochondrial inner membrane | 19/187 genes, 10.2% | 212/3725 genes, 5.7% | 8.95E-03 |
| Intracellular organelle part | 134/187 genes, 71.7% | 2361/3725 genes, 63.4% | 8.99E-03 |
| Nuclear matrix | 6/187 genes, 3.2% | 37/3725 genes, 1.0% | 9.34E-03 |
| Extracellular region part | 12/187 genes, 6.4% | 115/3725 genes, 3.1% | 1.17E-02 |
| PML body | 4/187 genes, 2.1% | 19/3725 genes, 0.5% | 1.32E-02 |
| Protein-DNA complex | 5/187 genes, 2.7% | 29/3725 genes, 0.8% | 1.34E-02 |
| Pericentriolar material | 2/187 genes, 1.1% | 4/3725 genes, 0.1% | 1.41E-02 |
| Telomere cap complex | 2/187 genes, 1.1% | 4/3725 genes, 0.1% | 1.41E-02 |
| Nuclear telomere cap complex | 2/187 genes, 1.1% | 4/3725 genes, 0.1% | 1.41E-02 |
| DNA-dependent protein kinase-DNA ligase 4 complex | 2/187 genes, 1.1% | 4/3725 genes, 0.1% | 1.41E-02 |
| Nonhomologous end joining complex | 2/187 genes, 1.1% | 4/3725 genes, 0.1% | 1.41E-02 |
| Proteasome accessory complex | 3/187 genes, 1.6% | 11/3725 genes, 0.3% | 1.52E-02 |
| Pronucleus | 3/187 genes, 1.6% | 11/3725 genes, 0.3% | 1.52E-02 |
| Extracellular matrix | 6/187 genes, 3.2% | 41/3725 genes, 1.1% | 1.53E-02 |
| Mitochondrial nucleoid | 5/187 genes, 2.7% | 30/3725 genes, 0.8% | 1.55E-02 |
| Endoplasmic reticulum lumen | 7/187 genes, 3.7% | 53/3725 genes, 1.4% | 1.56E-02 |
| Nuclear body | 12/187 genes, 6.4% | 120/3725 genes, 3.2% | 1.61E-02 |
| Cytosol | 67/187 genes, 35.8% | 1066/3725 genes, 28.6% | 1.69E-02 |
| Proteinaceous | 5/187 genes, 2.7% | 31/3725 genes, 0.8% | 1.77E-02 |

| | | | |
|-------------------------------|----------------------|------------------------|----------|
| extracellular matrix | | | |
| Extracellular matrix part | 4/187 genes, 2.1% | 21/3725 genes, 0.6% | 1.88E-02 |
| Preribosome | 3/187 genes, 1.6% | 12/3725 genes, 0.3% | 1.96E-02 |
| Spindle pole | 5/187 genes, 2.7% | 32/3725 genes, 0.9% | 2.02E-02 |
| Mitochondrial membrane part | 10/187 genes, 5.3% | 97/3725 genes, 2.6% | 2.23E-02 |
| Microtubule cytoskeleton | 22/187 genes, 11.8% | 281/3725 genes, 7.5% | 2.26E-02 |
| Collagen | 2/187 genes, 1.1% | 5/3725 genes, 0.1% | 2.27E-02 |
| Nucleoid | 5/187 genes, 2.7% | 33/3725 genes, 0.9% | 2.28E-02 |
| Nuclear heterochromatin | 3/187 genes, 1.6% | 13/3725 genes, 0.3% | 2.45E-02 |
| Cytoskeletal part | 27/187 genes, 14.4% | 368/3725 genes, 9.9% | 2.61E-02 |
| Chromatin | 10/187 genes, 5.3% | 100/3725 genes, 2.7% | 2.70E-02 |
| Ribosome | 12/187 genes, 6.4% | 129/3725 genes, 3.5% | 2.70E-02 |
| Microtubule organizing center | 13/187 genes, 7.0% | 146/3725 genes, 3.9% | 3.00E-02 |
| Intermediate filament | 4/187 genes, 2.1% | 25/3725 genes, 0.7% | 3.40E-02 |
| Cell | 186/187 genes, 99.5% | 3626/3725 genes, 97.3% | 3.63E-02 |
| Cell part | 186/187 genes, 99.5% | 3626/3725 genes, 97.3% | 3.63E-02 |
| Organelle envelope | 30/187 genes, 16.0% | 434/3725 genes, 11.7% | 3.98E-02 |
| Envelope | 30/187 genes, 16.0% | 435/3725 genes, 11.7% | 4.09E-02 |
| Cytoskeleton | 34/187 genes, 18.2% | 507/3725 genes, 13.6% | 4.29E-02 |
| Mitochondrial membrane | 21/187 genes, 11.2% | 284/3725 genes, 7.6% | 4.42E-02 |
| 90S preribosome | 2/187 genes, 1.1% | 7/3725 genes, 0.2% | 4.46E-02 |
| Paraspeckles | 2/187 genes, 1.1% | 7/3725 genes, 0.2% | 4.46E-02 |
| Midbody | 5/187 genes, 2.7% | 40/3725 genes, 1.1% | 4.78E-02 |
| Intracellular part | 182/187 genes, 97.3% | 3521/3725 genes, 94.5% | 4.95E-02 |

Supplementary Table S7. Gene ontology enrichment between E@TSN group and Control group (Function ontology) ($P < 0.05$).

| Gene ontology term | Cluster frequency | Protein frequency of use | <i>P</i> value |
|---------------------------------------------------|----------------------|--------------------------|----------------|
| Unfolded protein binding | 21/181 genes, 11.6% | 72/3499 genes, 2.1% | 2.40E-11 |
| Heterocyclic compound binding | 114/181 genes, 63.0% | 1513/3499 genes, 43.2% | 3.25E-08 |
| Organic cyclic compound binding | 114/181 genes, 63.0% | 1519/3499 genes, 43.4% | 4.25E-08 |
| Small molecule binding | 79/181 genes, 43.6% | 954/3499 genes, 27.3% | 8.30E-07 |
| Nucleotide binding | 76/181 genes, 42.0% | 920/3499 genes, 26.3% | 1.79E-06 |
| Nucleoside phosphate binding | 76/181 genes, 42.0% | 921/3499 genes, 26.3% | 1.88E-06 |
| Nucleic acid binding | 69/181 genes, 38.1% | 824/3499 genes, 23.5% | 4.66E-06 |
| RNA binding | 46/181 genes, 25.4% | 472/3499 genes, 13.5% | 7.29E-06 |
| Adenyl nucleotide binding | 49/181 genes, 27.1% | 524/3499 genes, 15.0% | 1.09E-05 |
| ATP binding | 48/181 genes, 26.5% | 517/3499 genes, 14.8% | 1.69E-05 |
| Purine nucleotide binding | 57/181 genes, 31.5% | 659/3499 genes, 18.8% | 1.86E-05 |
| Adenyl ribonucleotide binding | 48/181 genes, 26.5% | 521/3499 genes, 14.9% | 2.10E-05 |
| Purine ribonucleoside triphosphate binding | 56/181 genes, 30.9% | 651/3499 genes, 18.6% | 2.71E-05 |
| Purine ribonucleoside binding | 56/181 genes, 30.9% | 652/3499 genes, 18.6% | 2.84E-05 |
| Purine nucleoside binding | 56/181 genes, 30.9% | 653/3499 genes, 18.7% | 2.97E-05 |
| Ribonucleoside binding | 56/181 genes, 30.9% | 654/3499 genes, 18.7% | 3.11E-05 |
| Purine ribonucleotide binding | 56/181 genes, 30.9% | 654/3499 genes, 18.7% | 3.11E-05 |
| Nucleoside binding | 56/181 genes, 30.9% | 657/3499 genes, 18.8% | 3.58E-05 |
| Ribonucleotide binding | 56/181 genes, 30.9% | 659/3499 genes, 18.8% | 3.92E-05 |
| Translation factor activity, nucleic acid binding | 13/181 genes, 7.2% | 73/3499 genes, 2.1% | 6.91E-05 |
| Anion binding | 65/181 genes, 35.9% | 823/3499 genes, 23.5% | 7.74E-05 |
| Helicase activity | 12/181 genes, 6.6% | 68/3499 genes, 1.9% | 1.45E-04 |
| Atpase activity | 19/181 genes, 10.5% | 165/3499 genes, 4.7% | 6.95E-04 |
| ATP-dependent helicase activity | 10/181 genes, 5.5% | 60/3499 genes, 1.7% | 8.42E-04 |
| Purine NTP-dependent helicase activity | 10/181 genes, 5.5% | 60/3499 genes, 1.7% | 8.42E-04 |
| Cell surface binding | 4/181 genes, 2.2% | 10/3499 genes, 0.3% | 1.14E-03 |
| Pyrophosphatase activity | 30/181 genes, 16.6% | 331/3499 genes, 9.5% | 1.34E-03 |
| Hydrolase activity, acting on acid anhydrides | 30/181 genes, 16.6% | 331/3499 genes, 9.5% | 1.34E-03 |
| Hydrolase activity, acting on acid anhydrides, in | 30/181 genes, 16.6% | 331/3499 genes, 9.5% | 1.34E-03 |

| | | | |
|---------------------------------------------------------|----------------------|------------------------|----------|
| phosphorus-containing anhydrides | | | |
| Nucleoside-triphosphatase activity | 29/181 genes, 16.0% | 323/3499 genes, 9.2% | 1.89E-03 |
| Atpase activity, coupled | 15/181 genes, 8.3% | 128/3499 genes, 3.7% | 2.16E-03 |
| Chaperone binding | 6/181 genes, 3.3% | 28/3499 genes, 0.8% | 2.56E-03 |
| Fructose-bisphosphate aldolase activity | 2/181 genes, 1.1% | 2/3499 genes, 0.1% | 2.66E-03 |
| Lactate dehydrogenase activity | 2/181 genes, 1.1% | 2/3499 genes, 0.1% | 2.66E-03 |
| L-lactate dehydrogenase activity | 2/181 genes, 1.1% | 2/3499 genes, 0.1% | 2.66E-03 |
| Phosphotransferase activity, carboxyl group as acceptor | 2/181 genes, 1.1% | 2/3499 genes, 0.1% | 2.66E-03 |
| Purine deoxyribonucleotide binding | 2/181 genes, 1.1% | 2/3499 genes, 0.1% | 2.66E-03 |
| Adenyl deoxyribonucleotide binding | 2/181 genes, 1.1% | 2/3499 genes, 0.1% | 2.66E-03 |
| Datp binding | 2/181 genes, 1.1% | 2/3499 genes, 0.1% | 2.66E-03 |
| 5'-deoxyribose-5-phosphate lyase activity | 2/181 genes, 1.1% | 2/3499 genes, 0.1% | 2.66E-03 |
| Binding | 171/181 genes, 94.5% | 3085/3499 genes, 88.2% | 2.67E-03 |
| Telomeric DNA binding | 3/181 genes, 1.7% | 7/3499 genes, 0.2% | 4.08E-03 |
| Trna binding | 5/181 genes, 2.8% | 22/3499 genes, 0.6% | 4.49E-03 |
| DNA helicase activity | 5/181 genes, 2.8% | 22/3499 genes, 0.6% | 4.49E-03 |
| Translation elongation factor activity | 5/181 genes, 2.8% | 22/3499 genes, 0.6% | 4.49E-03 |
| Carboxylic acid binding | 9/181 genes, 5.0% | 63/3499 genes, 1.8% | 4.56E-03 |
| Single-stranded DNA binding | 7/181 genes, 3.9% | 43/3499 genes, 1.2% | 5.83E-03 |
| Translation initiation factor activity | 7/181 genes, 3.9% | 43/3499 genes, 1.2% | 5.83E-03 |
| Structure-specific DNA binding | 10/181 genes, 5.5% | 78/3499 genes, 2.2% | 6.25E-03 |
| Double-stranded telomeric DNA binding | 2/181 genes, 1.1% | 3/3499 genes, 0.1% | 7.71E-03 |
| Deoxyribonucleotide binding | 2/181 genes, 1.1% | 3/3499 genes, 0.1% | 7.71E-03 |
| Carbohydrate binding | 8/181 genes, 4.4% | 61/3499 genes, 1.7% | 1.23E-02 |
| Nitric-oxide synthase regulator activity | 2/181 genes, 1.1% | 4/3499 genes, 0.1% | 1.49E-02 |

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|-------------------------------------|-------------------|---------------------|----------|
| TPR domain binding | 2/181 genes, 1.1% | 4/3499 genes, 0.1% | 1.49E-02 |
| Eukaryotic cell surface binding | 2/181 genes, 1.1% | 4/3499 genes, 0.1% | 1.49E-02 |
| Receptor tyrosine kinase binding | 3/181 genes, 1.7% | 11/3499 genes, 0.3% | 1.65E-02 |
| ATP-dependent DNA helicase activity | 4/181 genes, 2.2% | 20/3499 genes, 0.6% | 1.75E-02 |
| Rrna binding | 4/181 genes, 2.2% | 20/3499 genes, 0.6% | 1.75E-02 |
| NAD binding | 6/181 genes, 3.3% | 41/3499 genes, 1.2% | 1.75E-02 |
| Monosaccharide binding | 5/181 genes, 2.8% | 32/3499 genes, 0.9% | 2.26E-02 |
| Phospholipase inhibitor activity | 2/181 genes, 1.1% | 5/3499 genes, 0.1% | 2.40E-02 |
| Lipase inhibitor activity | 2/181 genes, 1.1% | 5/3499 genes, 0.1% | 2.40E-02 |
| Aminoacyl-trna editing activity | 2/181 genes, 1.1% | 6/3499 genes, 0.2% | 3.48E-02 |
| Hsp70 protein binding | 2/181 genes, 1.1% | 6/3499 genes, 0.2% | 3.48E-02 |
| ADP binding | 3/181 genes, 1.7% | 15/3499 genes, 0.4% | 3.91E-02 |
| Protein binding, bridging | 5/181 genes, 2.8% | 37/3499 genes, 1.1% | 3.98E-02 |
| Mrna binding | 7/181 genes, 3.9% | 63/3499 genes, 1.8% | 4.22E-02 |
| Carbon-oxygen lyase activity | 4/181 genes, 2.2% | 26/3499 genes, 0.7% | 4.24E-02 |
| Structural constituent of ribosome | 9/181 genes, 5.0% | 92/3499 genes, 2.6% | 4.64E-02 |
| Solute: cation symporter activity | 2/181 genes, 1.1% | 7/3499 genes, 0.2% | 4.71E-02 |
| Aldehyde-lyase activity | 2/181 genes, 1.1% | 7/3499 genes, 0.2% | 4.71E-02 |
| Binding, bridging | 5/181 genes, 2.8% | 39/3499 genes, 1.1% | 4.84E-02 |

Supplementary Table S8. Gene ontology enrichment between E@TSN group and Control group (process ontology) ($P < 0.05$).

| Gene ontology term | Cluster frequency | Protein frequency of use | <i>P</i> value |
|--------------------------------------------------|----------------------|--------------------------|----------------|
| Protein folding | 24/183 genes, 13.1% | 127/3521 genes, 3.6% | 1.59E-08 |
| Response to unfolded protein | 14/183 genes, 7.7% | 62/3521 genes, 1.8% | 2.06E-06 |
| Response to topologically incorrect protein | 14/183 genes, 7.7% | 65/3521 genes, 1.8% | 3.77E-06 |
| Heterocycle metabolic process | 89/183 genes, 48.6% | 1173/3521 genes, 33.3% | 7.58E-06 |
| Nucleobase-containing compound metabolic process | 86/183 genes, 47.0% | 1122/3521 genes, 31.9% | 8.23E-06 |
| 'De novo' protein folding | 11/183 genes, 6.0% | 45/3521 genes, 1.3% | 1.19E-05 |
| Organic cyclic compound metabolic process | 91/183 genes, 49.7% | 1231/3521 genes, 35.0% | 1.77E-05 |
| 'De novo' posttranslational protein folding | 10/183 genes, 5.5% | 40/3521 genes, 1.1% | 2.44E-05 |
| Translational elongation | 13/183 genes, 7.1% | 68/3521 genes, 1.9% | 3.33E-05 |
| Chaperone-mediated protein complex assembly | 4/183 genes, 2.2% | 5/3521 genes, 0.1% | 3.39E-05 |
| Cellular aromatic compound metabolic process | 86/183 genes, 47.0% | 1164/3521 genes, 33.1% | 4.05E-05 |
| Cellular metabolic process | 139/183 genes, 76.0% | 2211/3521 genes, 62.8% | 6.96E-05 |
| Primary metabolic process | 138/183 genes, 75.4% | 2199/3521 genes, 62.5% | 9.32E-05 |
| Cellular nitrogen compound metabolic process | 90/183 genes, 49.2% | 1263/3521 genes, 35.9% | 1.03E-04 |
| Organic substance metabolic process | 140/183 genes, 76.5% | 2249/3521 genes, 63.9% | 1.18E-04 |
| Cellular macromolecule metabolic process | 104/183 genes, 56.8% | 1528/3521 genes, 43.4% | 1.21E-04 |
| Chaperone-mediated protein folding | 7/183 genes, 3.8% | 26/3521 genes, 0.7% | 2.59E-04 |
| Translational initiation | 12/183 genes, 6.6% | 72/3521 genes, 2.0% | 2.67E-04 |
| Macromolecule metabolic process | 108/183 genes, 59.0% | 1641/3521 genes, 46.6% | 3.64E-04 |
| Nucleic acid metabolic process | 63/183 genes, 34.4% | 829/3521 genes, 23.5% | 4.07E-04 |
| Protein refolding | 4/183 genes, 2.2% | 9/3521 genes, 0.3% | 7.24E-04 |
| Nitrogen compound metabolic process | 91/183 genes, 49.7% | 1346/3521 genes, 38.2% | 7.57E-04 |
| Metabolic process | 144/183 genes, 78.7% | 2413/3521 genes, 68.5% | 1.16E-03 |
| Cellular protein metabolic process | 66/183 genes, 36.1% | 923/3521 genes, 26.2% | 1.62E-03 |
| Gene expression | 54/183 genes, 29.5% | 722/3521 genes, 20.5% | 1.90E-03 |
| Ribosome biogenesis | 13/183 genes, 7.1% | 102/3521 genes, 2.9% | 2.09E-03 |

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|---------------------------------------------------------------------------------|---------------------|------------------------|----------|
| Viral infectious cycle | 10/183 genes, 5.5% | 68/3521 genes, 1.9% | 2.35E-03 |
| Regulation of deoxyribonuclease activity | 2/183 genes, 1.1% | 2/3521 genes, 0.1% | 2.69E-03 |
| Viral reproduction | 27/183 genes, 14.8% | 300/3521 genes, 8.5% | 2.84E-03 |
| Nuclear-transcribed mrna catabolic process, nonsense-mediated decay | 10/183 genes, 5.5% | 70/3521 genes, 2.0% | 2.92E-03 |
| Multi-organism cellular process | 27/183 genes, 14.8% | 301/3521 genes, 8.5% | 2.98E-03 |
| Mrna metabolic process | 32/183 genes, 17.5% | 379/3521 genes, 10.8% | 3.22E-03 |
| Translational termination | 8/183 genes, 4.4% | 49/3521 genes, 1.4% | 3.29E-03 |
| Viral genome expression | 8/183 genes, 4.4% | 49/3521 genes, 1.4% | 3.29E-03 |
| Viral transcription | 8/183 genes, 4.4% | 49/3521 genes, 1.4% | 3.29E-03 |
| Viral reproductive process | 22/183 genes, 12.0% | 230/3521 genes, 6.5% | 3.39E-03 |
| Translation | 20/183 genes, 10.9% | 204/3521 genes, 5.8% | 3.91E-03 |
| Protein metabolic process | 70/183 genes, 38.3% | 1025/3521 genes, 29.1% | 3.95E-03 |
| Chaperone mediated protein folding requiring cofactor | 3/183 genes, 1.6% | 7/3521 genes, 0.2% | 4.14E-03 |
| NAD metabolic process | 4/183 genes, 2.2% | 14/3521 genes, 0.4% | 4.69E-03 |
| Ribosome assembly | 4/183 genes, 2.2% | 14/3521 genes, 0.4% | 4.69E-03 |
| Cellular component biogenesis | 41/183 genes, 22.4% | 536/3521 genes, 15.2% | 5.22E-03 |
| Endoplasmic reticulum unfolded protein response | 7/183 genes, 3.8% | 42/3521 genes, 1.2% | 5.24E-03 |
| Cellular response to unfolded protein | 7/183 genes, 3.8% | 42/3521 genes, 1.2% | 5.24E-03 |
| Protein complex disassembly | 8/183 genes, 4.4% | 54/3521 genes, 1.5% | 6.07E-03 |
| Cellular protein complex disassembly | 8/183 genes, 4.4% | 54/3521 genes, 1.5% | 6.07E-03 |
| Macromolecular complex subunit organization | 36/183 genes, 19.7% | 459/3521 genes, 13.0% | 6.10E-03 |
| Negative regulation of intracellular steroid hormone receptor signaling pathway | 3/183 genes, 1.6% | 8/3521 genes, 0.2% | 6.37E-03 |
| Glycolysis | 5/183 genes, 2.7% | 24/3521 genes, 0.7% | 6.80E-03 |
| ER-nucleus signaling pathway | 7/183 genes, 3.8% | 44/3521 genes, 1.2% | 6.81E-03 |
| Cellular response to topologically incorrect protein | 7/183 genes, 3.8% | 44/3521 genes, 1.2% | 6.81E-03 |
| Multi-organism reproductive process | 23/183 genes, 12.6% | 259/3521 genes, 7.4% | 6.94E-03 |
| Nucleobase-containing compound biosynthetic process | 27/183 genes, 14.8% | 322/3521 genes, 9.1% | 7.56E-03 |

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|------------------------------------------------------------------------|----------------------|------------------------|----------|
| Morphogenesis of a polarized epithelium | 2/183 genes, 1.1% | 3/3521 genes, 0.1% | 7.79E-03 |
| Lactate metabolic process | 2/183 genes, 1.1% | 3/3521 genes, 0.1% | 7.79E-03 |
| Convergent extension | 2/183 genes, 1.1% | 3/3521 genes, 0.1% | 7.79E-03 |
| Macromolecular complex disassembly | 9/183 genes, 4.9% | 68/3521 genes, 1.9% | 7.83E-03 |
| Generation of precursor metabolites and energy | 18/183 genes, 9.8% | 188/3521 genes, 5.3% | 7.84E-03 |
| Regulation of intracellular steroid hormone receptor signaling pathway | 4/183 genes, 2.2% | 16/3521 genes, 0.5% | 7.85E-03 |
| Cellular process | 172/183 genes, 94.0% | 3118/3521 genes, 88.6% | 8.24E-03 |
| Glucose catabolic process | 6/183 genes, 3.3% | 35/3521 genes, 1.0% | 8.35E-03 |
| Cellular response to stress | 30/183 genes, 16.4% | 374/3521 genes, 10.6% | 9.16E-03 |
| Protein export from nucleus | 3/183 genes, 1.6% | 9/3521 genes, 0.3% | 9.19E-03 |
| RNA metabolic process | 46/183 genes, 25.1% | 638/3521 genes, 18.1% | 9.27E-03 |
| Response to stress | 51/183 genes, 27.9% | 724/3521 genes, 20.6% | 9.39E-03 |
| Regulation of nuclease activity | 6/183 genes, 3.3% | 37/3521 genes, 1.1% | 1.10E-02 |
| DNA metabolic process | 21/183 genes, 11.5% | 239/3521 genes, 6.8% | 1.10E-02 |
| Protein maturation | 5/183 genes, 2.7% | 27/3521 genes, 0.8% | 1.14E-02 |
| Cellular macromolecular complex assembly | 17/183 genes, 9.3% | 181/3521 genes, 5.1% | 1.16E-02 |
| Posttranscriptional regulation of gene expression | 15/183 genes, 8.2% | 153/3521 genes, 4.3% | 1.21E-02 |
| Response to endoplasmic reticulum stress | 7/183 genes, 3.8% | 49/3521 genes, 1.4% | 1.23E-02 |
| Glucose metabolic process | 9/183 genes, 4.9% | 73/3521 genes, 2.1% | 1.23E-02 |
| DNA conformation change | 8/183 genes, 4.4% | 61/3521 genes, 1.7% | 1.26E-02 |
| Protein complex subunit organization | 28/183 genes, 15.3% | 353/3521 genes, 10.0% | 1.36E-02 |
| Nucleotide metabolic process | 25/183 genes, 13.7% | 307/3521 genes, 8.7% | 1.44E-02 |
| Nucleoside phosphate metabolic process | 25/183 genes, 13.7% | 308/3521 genes, 8.7% | 1.50E-02 |
| Fructose 1,6-bisphosphate metabolic process | 2/183 genes, 1.1% | 4/3521 genes, 0.1% | 1.50E-02 |
| Chaperone cofactor-dependent protein refolding | 2/183 genes, 1.1% | 4/3521 genes, 0.1% | 1.50E-02 |
| Heterocycle biosynthetic process | 28/183 genes, 15.3% | 356/3521 genes, 10.1% | 1.52E-02 |
| DNA replication initiation | 3/183 genes, 1.6% | 11/3521 genes, 0.3% | 1.67E-02 |
| Ribonucleoprotein complex biogenesis | 15/183 genes, 8.2% | 160/3521 genes, 4.5% | 1.77E-02 |

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|--------------------------------------------------------|---------------------|-----------------------|----------|
| Pyridine nucleotide metabolic process | 5/183 genes, 2.7% | 30/3521 genes, 0.9% | 1.77E-02 |
| Monosaccharide biosynthetic process | 5/183 genes, 2.7% | 30/3521 genes, 0.9% | 1.77E-02 |
| Nicotinamide nucleotide metabolic process | 5/183 genes, 2.7% | 30/3521 genes, 0.9% | 1.77E-02 |
| Hexose catabolic process | 6/183 genes, 3.3% | 41/3521 genes, 1.2% | 1.79E-02 |
| Dicarboxylic acid metabolic process | 6/183 genes, 3.3% | 41/3521 genes, 1.2% | 1.79E-02 |
| Establishment of protein localization to organelle | 13/183 genes, 7.1% | 132/3521 genes, 3.7% | 1.83E-02 |
| Aromatic compound biosynthetic process | 27/183 genes, 14.8% | 346/3521 genes, 9.8% | 1.88E-02 |
| Ribonucleotide metabolic process | 19/183 genes, 10.4% | 222/3521 genes, 6.3% | 1.99E-02 |
| Nucleobase-containing small molecule metabolic process | 26/183 genes, 14.2% | 332/3521 genes, 9.4% | 2.02E-02 |
| Gluconeogenesis | 4/183 genes, 2.2% | 21/3521 genes, 0.6% | 2.11E-02 |
| Developmental growth involved in morphogenesis | 3/183 genes, 1.6% | 12/3521 genes, 0.3% | 2.15E-02 |
| Nuclear-transcribed mrna catabolic process | 11/183 genes, 6.0% | 107/3521 genes, 3.0% | 2.17E-02 |
| Monosaccharide catabolic process | 6/183 genes, 3.3% | 43/3521 genes, 1.2% | 2.22E-02 |
| Organelle assembly SRP-dependent | 6/183 genes, 3.3% | 43/3521 genes, 1.2% | 2.22E-02 |
| cotranslational protein targeting to membrane | 8/183 genes, 4.4% | 68/3521 genes, 1.9% | 2.32E-02 |
| Ribose phosphate metabolic process | 19/183 genes, 10.4% | 226/3521 genes, 6.4% | 2.35E-02 |
| Multi-organism process | 31/183 genes, 16.9% | 419/3521 genes, 11.9% | 2.42E-02 |
| Axis elongation | 2/183 genes, 1.1% | 5/3521 genes, 0.1% | 2.42E-02 |
| GMP biosynthetic process | 2/183 genes, 1.1% | 5/3521 genes, 0.1% | 2.42E-02 |
| DNA unwinding involved in replication | 2/183 genes, 1.1% | 5/3521 genes, 0.1% | 2.42E-02 |
| Outer mitochondrial membrane organization | 2/183 genes, 1.1% | 5/3521 genes, 0.1% | 2.42E-02 |
| Protein maturation by protein folding | 2/183 genes, 1.1% | 5/3521 genes, 0.1% | 2.42E-02 |
| Protein import into mitochondrial outer membrane | 2/183 genes, 1.1% | 5/3521 genes, 0.1% | 2.42E-02 |
| Mrna cis splicing, via spliceosome | 2/183 genes, 1.1% | 5/3521 genes, 0.1% | 2.42E-02 |

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|----------------------------------------------------------------|---------------------|-----------------------|----------|
| GMP metabolic process | 2/183 genes, 1.1% | 5/3521 genes, 0.1% | 2.42E-02 |
| Regulation of translation | 10/183 genes, 5.5% | 95/3521 genes, 2.7% | 2.42E-02 |
| Reproduction | 32/183 genes, 17.5% | 436/3521 genes, 12.4% | 2.45E-02 |
| Purine nucleotide metabolic process | 19/183 genes, 10.4% | 227/3521 genes, 6.4% | 2.45E-02 |
| Cotranslational protein targeting to membrane | 8/183 genes, 4.4% | 69/3521 genes, 2.0% | 2.52E-02 |
| Protein targeting to ER | 8/183 genes, 4.4% | 69/3521 genes, 2.0% | 2.52E-02 |
| Establishment of protein localization to endoplasmic reticulum | 8/183 genes, 4.4% | 69/3521 genes, 2.0% | 2.52E-02 |
| Nucleosome organization | 5/183 genes, 2.7% | 33/3521 genes, 0.9% | 2.60E-02 |
| Reproductive process | 30/183 genes, 16.4% | 405/3521 genes, 11.5% | 2.61E-02 |
| Purine ribonucleotide metabolic process | 18/183 genes, 9.8% | 214/3521 genes, 6.1% | 2.71E-02 |
| DNA packaging | 6/183 genes, 3.3% | 45/3521 genes, 1.3% | 2.73E-02 |
| Monosaccharide metabolic process | 10/183 genes, 5.5% | 97/3521 genes, 2.8% | 2.76E-02 |
| Mrna catabolic process | 11/183 genes, 6.0% | 111/3521 genes, 3.2% | 2.77E-02 |
| Protein targeting to membrane | 9/183 genes, 4.9% | 84/3521 genes, 2.4% | 2.87E-02 |
| Organic cyclic compound biosynthetic process | 29/183 genes, 15.8% | 392/3521 genes, 11.1% | 2.90E-02 |
| Purine nucleotide biosynthetic process | 7/183 genes, 3.8% | 58/3521 genes, 1.6% | 2.91E-02 |
| Heterocycle catabolic process | 26/183 genes, 14.2% | 343/3521 genes, 9.7% | 2.92E-02 |
| Chromatin assembly or disassembly | 5/183 genes, 2.7% | 34/3521 genes, 1.0% | 2.93E-02 |
| Positive regulation of nuclease activity | 5/183 genes, 2.7% | 34/3521 genes, 1.0% | 2.93E-02 |
| Pyridine-containing compound metabolic process | 5/183 genes, 2.7% | 34/3521 genes, 1.0% | 2.93E-02 |
| Cellular component assembly | 32/183 genes, 17.5% | 443/3521 genes, 12.6% | 3.00E-02 |
| Protein localization to organelle | 17/183 genes, 9.3% | 202/3521 genes, 5.7% | 3.12E-02 |
| Cellular macromolecule biosynthetic process | 37/183 genes, 20.2% | 529/3521 genes, 15.0% | 3.12E-02 |
| Oxidoreduction coenzyme metabolic process | 5/183 genes, 2.7% | 35/3521 genes, 1.0% | 3.28E-02 |
| Visual perception | 3/183 genes, 1.6% | 14/3521 genes, 0.4% | 3.29E-02 |
| DNA duplex unwinding | 3/183 genes, 1.6% | 14/3521 genes, 0.4% | 3.29E-02 |
| Ribosomal small subunit biogenesis | 3/183 genes, 1.6% | 14/3521 genes, 0.4% | 3.29E-02 |

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|----------------------------------------------------------|---------------------|------------------------|----------|
| Sensory perception of light stimulus | 3/183 genes, 1.6% | 14/3521 genes, 0.4% | 3.29E-02 |
| DNA strand elongation involved in DNA replication | 4/183 genes, 2.2% | 24/3521 genes, 0.7% | 3.32E-02 |
| Nucleosome assembly | 4/183 genes, 2.2% | 24/3521 genes, 0.7% | 3.32E-02 |
| Hexose biosynthetic process | 4/183 genes, 2.2% | 24/3521 genes, 0.7% | 3.32E-02 |
| DNA strand elongation | 4/183 genes, 2.2% | 24/3521 genes, 0.7% | 3.32E-02 |
| Intracellular steroid hormone receptor signaling pathway | 4/183 genes, 2.2% | 24/3521 genes, 0.7% | 3.32E-02 |
| Cellular component organization or biogenesis | 77/183 genes, 42.1% | 1248/3521 genes, 35.4% | 3.34E-02 |
| Mitochondrial transport | 8/183 genes, 4.4% | 73/3521 genes, 2.1% | 3.40E-02 |
| Macromolecular complex assembly | 26/183 genes, 14.2% | 348/3521 genes, 9.9% | 3.43E-02 |
| Ribonucleoside triphosphate metabolic process | 16/183 genes, 8.7% | 189/3521 genes, 5.4% | 3.44E-02 |
| Interaction with host | 16/183 genes, 8.7% | 189/3521 genes, 5.4% | 3.44E-02 |
| Non-recombinational repair | 2/183 genes, 1.1% | 6/3521 genes, 0.2% | 3.51E-02 |
| Fructose metabolic process | 2/183 genes, 1.1% | 6/3521 genes, 0.2% | 3.51E-02 |
| Double-strand break repair via nonhomologous end joining | 2/183 genes, 1.1% | 6/3521 genes, 0.2% | 3.51E-02 |
| DNA replication-independent nucleosome assembly | 2/183 genes, 1.1% | 6/3521 genes, 0.2% | 3.51E-02 |
| Dosage compensation | 2/183 genes, 1.1% | 6/3521 genes, 0.2% | 3.51E-02 |
| Mitochondrial fusion | 2/183 genes, 1.1% | 6/3521 genes, 0.2% | 3.51E-02 |
| Regulation of centrosome duplication | 2/183 genes, 1.1% | 6/3521 genes, 0.2% | 3.51E-02 |
| Protein sumoylation | 2/183 genes, 1.1% | 6/3521 genes, 0.2% | 3.51E-02 |
| 4-hydroxyproline metabolic process | 2/183 genes, 1.1% | 6/3521 genes, 0.2% | 3.51E-02 |
| CENP-A containing nucleosome assembly at centromere | 2/183 genes, 1.1% | 6/3521 genes, 0.2% | 3.51E-02 |
| DNA replication-independent nucleosome organization | 2/183 genes, 1.1% | 6/3521 genes, 0.2% | 3.51E-02 |
| Branching involved in mammary gland duct morphogenesis | 2/183 genes, 1.1% | 6/3521 genes, 0.2% | 3.51E-02 |
| Mammary gland duct morphogenesis | 2/183 genes, 1.1% | 6/3521 genes, 0.2% | 3.51E-02 |
| DNA biosynthetic process | 2/183 genes, 1.1% | 6/3521 genes, 0.2% | 3.51E-02 |
| Establishment of epithelial cell polarity | 2/183 genes, 1.1% | 6/3521 genes, 0.2% | 3.51E-02 |

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|------------------------------------------------------------------------------------|---------------------|-----------------------|----------|
| Negative regulation of cellular macromolecule biosynthetic process | 18/183 genes, 9.8% | 221/3521 genes, 6.3% | 3.59E-02 |
| Intracellular receptor mediated signaling pathway | 6/183 genes, 3.3% | 48/3521 genes, 1.4% | 3.62E-02 |
| Nucleoside metabolic process | 19/183 genes, 10.4% | 237/3521 genes, 6.7% | 3.63E-02 |
| Cellular nitrogen compound biosynthetic process | 28/183 genes, 15.3% | 383/3521 genes, 10.9% | 3.64E-02 |
| Protein localization to endoplasmic reticulum | 8/183 genes, 4.4% | 74/3521 genes, 2.1% | 3.64E-02 |
| Virus-host interaction | 15/183 genes, 8.2% | 176/3521 genes, 5.0% | 3.79E-02 |
| Chromatin assembly | 4/183 genes, 2.2% | 25/3521 genes, 0.7% | 3.79E-02 |
| Negative regulation of sequence-specific DNA binding transcription factor activity | 4/183 genes, 2.2% | 25/3521 genes, 0.7% | 3.79E-02 |
| Organic cyclic compound catabolic process | 26/183 genes, 14.2% | 352/3521 genes, 10.0% | 3.87E-02 |
| Symbiosis, encompassing mutualism through parasitism | 16/183 genes, 8.7% | 192/3521 genes, 5.5% | 3.90E-02 |
| Interspecies interaction between organisms | 16/183 genes, 8.7% | 192/3521 genes, 5.5% | 3.90E-02 |
| DNA geometric change | 3/183 genes, 1.6% | 15/3521 genes, 0.4% | 3.96E-02 |
| RNA catabolic process | 11/183 genes, 6.0% | 118/3521 genes, 3.4% | 4.10E-02 |
| Negative regulation of transcription, DNA-dependent | 15/183 genes, 8.2% | 178/3521 genes, 5.1% | 4.13E-02 |
| Regulation of biosynthetic process | 46/183 genes, 25.1% | 697/3521 genes, 19.8% | 4.13E-02 |
| RNA processing | 27/183 genes, 14.8% | 371/3521 genes, 10.5% | 4.17E-02 |
| Purine-containing compound metabolic process | 19/183 genes, 10.4% | 241/3521 genes, 6.8% | 4.20E-02 |
| Organic substance biosynthetic process | 55/183 genes, 30.1% | 858/3521 genes, 24.4% | 4.21E-02 |
| Hexose metabolic process | 9/183 genes, 4.9% | 90/3521 genes, 2.6% | 4.23E-02 |
| Mitochondrial membrane organization | 4/183 genes, 2.2% | 26/3521 genes, 0.7% | 4.31E-02 |
| Ribonucleotide biosynthetic process | 7/183 genes, 3.8% | 63/3521 genes, 1.8% | 4.31E-02 |
| Ribonucleoside metabolic process | 18/183 genes, 9.8% | 226/3521 genes, 6.4% | 4.34E-02 |
| Protein-DNA complex subunit organization | 5/183 genes, 2.7% | 38/3521 genes, 1.1% | 4.47E-02 |

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|----------------------------------------------------------------------------------------|---------------------|-----------------------|----------|
| Glycosyl compound metabolic process | 19/183 genes, 10.4% | 243/3521 genes, 6.9% | 4.52E-02 |
| Macromolecule biosynthetic process | 37/183 genes, 20.2% | 544/3521 genes, 15.5% | 4.54E-02 |
| Nucleoside triphosphate metabolic process | 16/183 genes, 8.7% | 196/3521 genes, 5.6% | 4.58E-02 |
| Chromatin remodeling at centromere | 2/183 genes, 1.1% | 7/3521 genes, 0.2% | 4.75E-02 |
| Histone exchange Establishment or maintenance of epithelial cell apical/basal polarity | 2/183 genes, 1.1% | 7/3521 genes, 0.2% | 4.75E-02 |
| Mitochondrion localization | 2/183 genes, 1.1% | 7/3521 genes, 0.2% | 4.75E-02 |
| Mammary gland morphogenesis | 2/183 genes, 1.1% | 7/3521 genes, 0.2% | 4.75E-02 |
| Negative regulation of macromolecule biosynthetic process | 18/183 genes, 9.8% | 229/3521 genes, 6.5% | 4.84E-02 |
| Protein stabilization | 4/183 genes, 2.2% | 27/3521 genes, 0.8% | 4.86E-02 |
| Regulation of cellular biosynthetic process | 45/183 genes, 24.6% | 687/3521 genes, 19.5% | 4.88E-02 |
| Protein targeting to mitochondrion | 5/183 genes, 2.7% | 39/3521 genes, 1.1% | 4.93E-02 |
| Purine ribonucleoside metabolic process | 17/183 genes, 9.3% | 214/3521 genes, 6.1% | 4.99E-02 |
| Aromatic compound catabolic process | 25/183 genes, 13.7% | 344/3521 genes, 9.8% | 4.99E-02 |
| Cellular nitrogen compound catabolic process | 25/183 genes, 13.7% | 344/3521 genes, 9.8% | 4.99E-02 |

Supplementary Table S9. Gene ontology enrichment between EA group and Control group (component ontology) ($P < 0.05$).

| Gene ontology term | Cluster frequency | Protein frequency of use | <i>P</i> value |
|----------------------------------------------|---------------------|--------------------------|----------------|
| Extracellular region part | 15/118 genes, 12.7% | 115/3725 genes, 3.1% | 2.22E-06 |
| Cell-cell junction | 12/118 genes, 10.2% | 93/3725 genes, 2.5% | 2.77E-05 |
| Extracellular region | 18/118 genes, 15.3% | 199/3725 genes, 5.3% | 3.98E-05 |
| MCM complex | 4/118 genes, 3.4% | 8/3725 genes, 0.2% | 6.07E-05 |
| Cell junction | 16/118 genes, 13.6% | 182/3725 genes, 4.9% | 1.57E-04 |
| Extracellular organelle | 3/118 genes, 2.5% | 5/3725 genes, 0.1% | 2.96E-04 |
| Extracellular membrane-bounded organelle | 3/118 genes, 2.5% | 5/3725 genes, 0.1% | 2.96E-04 |
| Extracellular vesicular exosome | 3/118 genes, 2.5% | 5/3725 genes, 0.1% | 2.96E-04 |
| Non-membrane-bounded organelle | 60/118 genes, 50.8% | 1324/3725 genes, 35.5% | 3.83E-04 |
| Intracellular non-membrane-bounded organelle | 60/118 genes, 50.8% | 1324/3725 genes, 35.5% | 3.83E-04 |
| Condensin complex | 3/118 genes, 2.5% | 6/3725 genes, 0.2% | 5.78E-04 |
| Cell-cell adherens junction | 5/118 genes, 4.2% | 24/3725 genes, 0.6% | 7.68E-04 |
| Intermediate filament cytoskeleton | 6/118 genes, 5.1% | 36/3725 genes, 1.0% | 7.96E-04 |
| Melanosome | 8/118 genes, 6.8% | 64/3725 genes, 1.7% | 8.02E-04 |
| Pigment granule | 8/118 genes, 6.8% | 64/3725 genes, 1.7% | 8.02E-04 |
| Intermediate filament | 5/118 genes, 4.2% | 25/3725 genes, 0.7% | 9.36E-04 |
| Extracellular space | 9/118 genes, 7.6% | 85/3725 genes, 2.3% | 1.29E-03 |
| Cell surface | 9/118 genes, 7.6% | 86/3725 genes, 2.3% | 1.40E-03 |
| Extracellular matrix | 6/118 genes, 5.1% | 41/3725 genes, 1.1% | 1.61E-03 |
| Cytoskeleton | 28/118 genes, 23.7% | 507/3725 genes, 13.6% | 1.77E-03 |

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|------------------------------------|----------------------|------------------------|----------|
| Proteinaceous extracellular matrix | 5/118 genes, 4.2% | 31/3725 genes, 0.8% | 2.57E-03 |
| Cornified envelope | 2/118 genes, 1.7% | 3/3725 genes, 0.1% | 2.92E-03 |
| Anchoring junction | 8/118 genes, 6.8% | 79/3725 genes, 2.1% | 3.18E-03 |
| Desmosome | 3/118 genes, 2.5% | 13/3725 genes, 0.3% | 7.03E-03 |
| Adherens junction | 7/118 genes, 5.9% | 73/3725 genes, 2.0% | 7.73E-03 |
| Intercalated disc | 3/118 genes, 2.5% | 14/3725 genes, 0.4% | 8.74E-03 |
| Cell-cell contact zone | 3/118 genes, 2.5% | 14/3725 genes, 0.4% | 8.74E-03 |
| Contractile fiber part | 5/118 genes, 4.2% | 41/3725 genes, 1.1% | 8.82E-03 |
| Collagen | 2/118 genes, 1.7% | 5/3725 genes, 0.1% | 9.35E-03 |
| Intracellular part | 117/118 genes, 99.2% | 3521/3725 genes, 94.5% | 9.40E-03 |
| Plasma membrane | 31/118 genes, 26.3% | 652/3725 genes, 17.5% | 1.00E-02 |
| Cytoskeletal part | 20/118 genes, 16.9% | 368/3725 genes, 9.9% | 1.05E-02 |
| Cell periphery | 32/118 genes, 27.1% | 682/3725 genes, 18.3% | 1.07E-02 |
| Coated pit | 4/118 genes, 3.4% | 28/3725 genes, 0.8% | 1.09E-02 |
| Macromolecular complex | 61/118 genes, 51.7% | 1533/3725 genes, 41.2% | 1.21E-02 |
| Myofibril | 5/118 genes, 4.2% | 45/3725 genes, 1.2% | 1.30E-02 |
| Nucleolus | 30/118 genes, 25.4% | 639/3725 genes, 17.2% | 1.36E-02 |
| Cytosol | 45/118 genes, 38.1% | 1066/3725 genes, 28.6% | 1.48E-02 |
| Cytosolic part | 8/118 genes, 6.8% | 103/3725 genes, 2.8% | 1.54E-02 |
| Contractile fiber | 5/118 genes, 4.2% | 47/3725 genes, 1.3% | 1.55E-02 |
| Chaperonin-containing complex | 2/118 genes, 1.7% | 7/3725 genes, 0.2% | 1.88E-02 |
| Fascia adherens | 2/118 genes, 1.7% | 7/3725 genes, 0.2% | 1.88E-02 |

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|--------------------------------------|----------------------|------------------------|----------|
| Microtubule | 8/118 genes, 6.8% | 109/3725 genes, 2.9% | 2.11E-02 |
| Sarcomere | 4/118 genes, 3.4% | 34/3725 genes, 0.9% | 2.13E-02 |
| Ribonucleoprotein complex | 19/118 genes, 16.1% | 369/3725 genes, 9.9% | 2.15E-02 |
| Plasma membrane part | 17/118 genes, 14.4% | 319/3725 genes, 8.6% | 2.17E-02 |
| Intracellular | 117/118 genes, 99.2% | 3551/3725 genes, 95.3% | 2.25E-02 |
| Nucleosome | 2/118 genes, 1.7% | 8/3725 genes, 0.2% | 2.46E-02 |
| Endoplasmic reticulum lumen | 5/118 genes, 4.2% | 53/3725 genes, 1.4% | 2.50E-02 |
| Extracellular matrix part | 3/118 genes, 2.5% | 21/3725 genes, 0.6% | 2.72E-02 |
| Membrane-bounded vesicle | 15/118 genes, 12.7% | 278/3725 genes, 7.5% | 2.77E-02 |
| Condensed chromosome | 6/118 genes, 5.1% | 74/3725 genes, 2.0% | 2.86E-02 |
| Z disc | 3/118 genes, 2.5% | 22/3725 genes, 0.6% | 3.08E-02 |
| Sarcolemma | 3/118 genes, 2.5% | 22/3725 genes, 0.6% | 3.08E-02 |
| I band | 3/118 genes, 2.5% | 23/3725 genes, 0.6% | 3.46E-02 |
| Midbody | 4/118 genes, 3.4% | 40/3725 genes, 1.1% | 3.64E-02 |
| Nuclear lamina | 2/118 genes, 1.7% | 10/3725 genes, 0.3% | 3.79E-02 |
| Plasma lipoprotein particle | 2/118 genes, 1.7% | 10/3725 genes, 0.3% | 3.79E-02 |
| Costamere | 2/118 genes, 1.7% | 10/3725 genes, 0.3% | 3.79E-02 |
| Basolateral plasma membrane | 4/118 genes, 3.4% | 41/3725 genes, 1.1% | 3.93E-02 |
| Cytoplasmic membrane-bounded vesicle | 14/118 genes, 11.9% | 271/3725 genes, 7.3% | 4.53E-02 |
| Protein-lipid complex | 2/118 genes, 1.7% | 11/3725 genes, 0.3% | 4.54E-02 |
| Pronucleus | 2/118 genes, 1.7% | 11/3725 genes, 0.3% | 4.54E-02 |

Supplementary Table S10. Gene ontology enrichment between EA group and Control group (function ontology) ($P < 0.05$).

| Gene ontology term | Cluster frequency | Protein frequency of use | <i>P</i> value |
|------------------------------------------------------------------------------------|---------------------|--------------------------|----------------|
| ATP binding | 35/118 genes, 29.7% | 517/3499 genes, 14.8% | 1.95E-05 |
| Adenyl ribonucleotide binding | 35/118 genes, 29.7% | 521/3499 genes, 14.9% | 2.31E-05 |
| Adenyl nucleotide binding | 35/118 genes, 29.7% | 524/3499 genes, 15.0% | 2.63E-05 |
| Purine ribonucleoside triphosphate binding | 39/118 genes, 33.1% | 651/3499 genes, 18.6% | 9.78E-05 |
| Purine ribonucleoside binding | 39/118 genes, 33.1% | 652/3499 genes, 18.6% | 1.01E-04 |
| Purine nucleoside binding | 39/118 genes, 33.1% | 653/3499 genes, 18.7% | 1.05E-04 |
| Ribonucleoside binding | 39/118 genes, 33.1% | 654/3499 genes, 18.7% | 1.09E-04 |
| Purine ribonucleotide binding | 39/118 genes, 33.1% | 654/3499 genes, 18.7% | 1.09E-04 |
| Unfolded protein binding | 10/118 genes, 8.5% | 72/3499 genes, 2.1% | 1.19E-04 |
| Nucleoside binding | 39/118 genes, 33.1% | 657/3499 genes, 18.8% | 1.20E-04 |
| Purine nucleotide binding | 39/118 genes, 33.1% | 659/3499 genes, 18.8% | 1.29E-04 |
| Ribonucleotide binding | 39/118 genes, 33.1% | 659/3499 genes, 18.8% | 1.29E-04 |
| Anion binding | 45/118 genes, 38.1% | 823/3499 genes, 23.5% | 2.13E-04 |
| ATPase activity, coupled | 13/118 genes, 11.0% | 128/3499 genes, 3.7% | 2.99E-04 |
| ATPase activity | 15/118 genes, 12.7% | 165/3499 genes, 4.7% | 3.47E-04 |
| Helicase activity | 9/118 genes, 7.6% | 68/3499 genes, 1.9% | 3.83E-04 |
| Small molecule binding | 49/118 genes, 41.5% | 954/3499 genes, 27.3% | 4.65E-04 |
| ATP-dependent helicase activity | 8/118 genes, 6.8% | 60/3499 genes, 1.7% | 7.77E-04 |
| Purine NTP-dependent helicase activity | 8/118 genes, 6.8% | 60/3499 genes, 1.7% | 7.77E-04 |
| Fructose-bisphosphate aldolase activity | 2/118 genes, 1.7% | 2/3499 genes, 0.1% | 1.13E-03 |
| Phosphotransferase activity, carboxyl group as acceptor | 2/118 genes, 1.7% | 2/3499 genes, 0.1% | 1.13E-03 |
| Nucleotide binding | 45/118 genes, 38.1% | 920/3499 genes, 26.3% | 2.75E-03 |
| Nucleoside phosphate binding | 45/118 genes, 38.1% | 921/3499 genes, 26.3% | 2.81E-03 |
| Single-stranded DNA binding | 6/118 genes, 5.1% | 43/3499 genes, 1.2% | 2.84E-03 |
| Pyrophosphatase activity | 21/118 genes, 17.8% | 331/3499 genes, 9.5% | 2.95E-03 |
| Hydrolase activity, acting on acid anhydrides | 21/118 genes, 17.8% | 331/3499 genes, 9.5% | 2.95E-03 |
| Hydrolase activity, acting on acid anhydrides, in phosphorus-containing anhydrides | 21/118 genes, 17.8% | 331/3499 genes, 9.5% | 2.95E-03 |
| Cell surface binding | 3/118 genes, 2.5% | 10/3499 genes, 0.3% | 3.77E-03 |
| Actin filament binding | 5/118 genes, 4.2% | 32/3499 genes, 0.9% | 3.89E-03 |
| Carbohydrate binding | 7/118 genes, 5.9% | 61/3499 genes, 1.7% | 4.00E-03 |
| Nucleoside-triphosphatase activity | 20/118 genes, 16.9% | 323/3499 genes, 9.2% | 4.95E-03 |

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|-----------------------------------------------------------------------------|----------------------|------------------------|----------|
| Structural constituent of cytoskeleton | 5/118 genes, 4.2% | 34/3499 genes, 1.0% | 5.09E-03 |
| Cytoskeletal protein binding | 14/118 genes, 11.9% | 199/3499 genes, 5.7% | 6.35E-03 |
| Nitric-oxide synthase regulator activity | 2/118 genes, 1.7% | 4/3499 genes, 0.1% | 6.47E-03 |
| TPR domain binding | 2/118 genes, 1.7% | 4/3499 genes, 0.1% | 6.47E-03 |
| Xenobiotic transporter activity | 2/118 genes, 1.7% | 4/3499 genes, 0.1% | 6.47E-03 |
| Cadherin binding | 3/118 genes, 2.5% | 12/3499 genes, 0.3% | 6.58E-03 |
| Structural molecule activity | 14/118 genes, 11.9% | 201/3499 genes, 5.7% | 6.93E-03 |
| Heterocyclic compound binding | 64/118 genes, 54.2% | 1513/3499 genes, 43.2% | 9.45E-03 |
| Organic cyclic compound binding | 64/118 genes, 54.2% | 1519/3499 genes, 43.4% | 1.05E-02 |
| Phospholipase inhibitor activity | 2/118 genes, 1.7% | 5/3499 genes, 0.1% | 1.05E-02 |
| Lipase inhibitor activity | 2/118 genes, 1.7% | 5/3499 genes, 0.1% | 1.05E-02 |
| ADP binding | 3/118 genes, 2.5% | 15/3499 genes, 0.4% | 1.26E-02 |
| Structure-specific DNA binding | 7/118 genes, 5.9% | 78/3499 genes, 2.2% | 1.51E-02 |
| Intramolecular oxidoreductase activity | 4/118 genes, 3.4% | 29/3499 genes, 0.8% | 1.52E-02 |
| Actin binding | 9/118 genes, 7.6% | 117/3499 genes, 3.3% | 1.61E-02 |
| Aldehyde-lyase activity | 2/118 genes, 1.7% | 7/3499 genes, 0.2% | 2.12E-02 |
| Monosaccharide binding | 4/118 genes, 3.4% | 32/3499 genes, 0.9% | 2.13E-02 |
| Binding | 111/118 genes, 94.1% | 3085/3499 genes, 88.2% | 2.34E-02 |
| Cell adhesion molecule binding | 3/118 genes, 2.5% | 19/3499 genes, 0.5% | 2.44E-02 |
| Microfilament motor activity | 2/118 genes, 1.7% | 8/3499 genes, 0.2% | 2.76E-02 |
| L-ascorbic acid binding | 2/118 genes, 1.7% | 8/3499 genes, 0.2% | 2.76E-02 |
| ATP-dependent DNA helicase activity | 3/118 genes, 2.5% | 20/3499 genes, 0.6% | 2.80E-02 |
| Ion binding | 57/118 genes, 48.3% | 1378/3499 genes, 39.4% | 2.81E-02 |
| Intramolecular oxidoreductase activity, interconverting aldoses and ketoses | 2/118 genes, 1.7% | 9/3499 genes, 0.3% | 3.48E-02 |
| Trna binding | 3/118 genes, 2.5% | 22/3499 genes, 0.6% | 3.61E-02 |
| DNA helicase activity | 3/118 genes, 2.5% | 22/3499 genes, 0.6% | 3.61E-02 |
| Carbon-carbon lyase activity | 3/118 genes, 2.5% | 22/3499 genes, 0.6% | 3.61E-02 |
| Calcium-dependent phospholipid binding | 2/118 genes, 1.7% | 10/3499 genes, 0.3% | 4.25E-02 |
| Structural constituent of muscle | 2/118 genes, 1.7% | 10/3499 genes, 0.3% | 4.25E-02 |

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|-------------------------------------------------------------------------------|---------------------|------------------------|----------|
| Intramolecular oxidoreductase activity, interconverting keto- and enol-groups | 2/118 genes, 1.7% | 10/3499 genes, 0.3% | 4.25E-02 |
| Protein binding | 87/118 genes, 73.7% | 2312/3499 genes, 66.1% | 4.37E-02 |
| Calmodulin binding | 4/118 genes, 3.4% | 41/3499 genes, 1.2% | 4.77E-02 |
| Isomerase activity | 6/118 genes, 5.1% | 79/3499 genes, 2.3% | 4.88E-02 |

Supplementary Table S11. Gene ontology enrichment between EA group and Control group (process ontology) ($P < 0.05$).

| Gene ontology term | Cluster frequency | Protein frequency of use | <i>P</i> value |
|---------------------------------------------------|---------------------|--------------------------|----------------|
| Glycolysis | 8/120 genes, 6.7% | 24/3521 genes, 0.7% | 6.71E-07 |
| Response to unfolded protein | 12/120 genes, 10.0% | 62/3521 genes, 1.8% | 7.23E-07 |
| Response to topologically incorrect protein | 12/120 genes, 10.0% | 65/3521 genes, 1.8% | 1.24E-06 |
| Gluconeogenesis | 7/120 genes, 5.8% | 21/3521 genes, 0.6% | 3.51E-06 |
| Hexose biosynthetic process | 7/120 genes, 5.8% | 24/3521 genes, 0.7% | 9.59E-06 |
| Glucose catabolic process | 8/120 genes, 6.7% | 35/3521 genes, 1.0% | 1.57E-05 |
| Protein folding | 15/120 genes, 12.5% | 127/3521 genes, 3.6% | 1.89E-05 |
| Glucose metabolic process | 11/120 genes, 9.2% | 73/3521 genes, 2.1% | 2.70E-05 |
| DNA conformation change | 10/120 genes, 8.3% | 61/3521 genes, 1.7% | 3.01E-05 |
| Monosaccharide biosynthetic process | 7/120 genes, 5.8% | 30/3521 genes, 0.9% | 4.76E-05 |
| Hexose catabolic process | 8/120 genes, 6.7% | 41/3521 genes, 1.2% | 5.36E-05 |
| Monosaccharide catabolic process | 8/120 genes, 6.7% | 43/3521 genes, 1.2% | 7.68E-05 |
| Monosaccharide metabolic process | 12/120 genes, 10.0% | 97/3521 genes, 2.8% | 8.66E-05 |
| Hexose metabolic process | 11/120 genes, 9.2% | 90/3521 genes, 2.6% | 1.93E-04 |
| System development | 38/120 genes, 31.7% | 647/3521 genes, 18.4% | 2.51E-04 |
| DNA replication initiation | 4/120 genes, 3.3% | 11/3521 genes, 0.3% | 3.52E-04 |
| Carbohydrate biosynthetic process | 8/120 genes, 6.7% | 53/3521 genes, 1.5% | 3.53E-04 |
| DNA unwinding involved in replication | 3/120 genes, 2.5% | 5/3521 genes, 0.1% | 3.67E-04 |
| Chaperone-mediated protein complex assembly | 3/120 genes, 2.5% | 5/3521 genes, 0.1% | 3.67E-04 |
| Single-organism carbohydrate catabolic process | 8/120 genes, 6.7% | 54/3521 genes, 1.5% | 4.03E-04 |
| Carbohydrate catabolic process | 8/120 genes, 6.7% | 55/3521 genes, 1.6% | 4.58E-04 |
| DNA packaging | 7/120 genes, 5.8% | 45/3521 genes, 1.3% | 6.93E-04 |
| Developmental process | 45/120 genes, 37.5% | 863/3521 genes, 24.5% | 8.74E-04 |
| DNA strand elongation involved in DNA replication | 5/120 genes, 4.2% | 24/3521 genes, 0.7% | 1.07E-03 |
| DNA strand elongation | 5/120 genes, 4.2% | 24/3521 genes, 0.7% | 1.07E-03 |
| Anatomical structure development | 41/120 genes, 34.2% | 769/3521 genes, 21.8% | 1.07E-03 |

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|-------------------------------------------------------|---------------------|------------------------|----------|
| Regulation of deoxyribonuclease activity | 2/120 genes, 1.7% | 2/3521 genes, 0.1% | 1.15E-03 |
| Mitotic chromosome condensation | 3/120 genes, 2.5% | 7/3521 genes, 0.2% | 1.22E-03 |
| Chaperone mediated protein folding requiring cofactor | 3/120 genes, 2.5% | 7/3521 genes, 0.2% | 1.22E-03 |
| Response to chemical stimulus | 39/120 genes, 32.5% | 725/3521 genes, 20.6% | 1.26E-03 |
| Regulation of nuclease activity | 6/120 genes, 5.0% | 37/3521 genes, 1.1% | 1.35E-03 |
| Cell cycle phase transition | 9/120 genes, 7.5% | 83/3521 genes, 2.4% | 1.80E-03 |
| Mitotic cell cycle phase transition | 9/120 genes, 7.5% | 83/3521 genes, 2.4% | 1.80E-03 |
| Multicellular organismal development | 40/120 genes, 33.3% | 764/3521 genes, 21.7% | 1.83E-03 |
| Response to organic substance | 30/120 genes, 25.0% | 522/3521 genes, 14.8% | 2.01E-03 |
| Response to stress | 38/120 genes, 31.7% | 724/3521 genes, 20.6% | 2.40E-03 |
| Response to stimulus | 63/120 genes, 52.5% | 1398/3521 genes, 39.7% | 2.63E-03 |
| Endoplasmic reticulum unfolded protein response | 6/120 genes, 5.0% | 42/3521 genes, 1.2% | 2.65E-03 |
| Cellular response to unfolded protein | 6/120 genes, 5.0% | 42/3521 genes, 1.2% | 2.65E-03 |
| ER-nucleus signaling pathway | 6/120 genes, 5.0% | 44/3521 genes, 1.2% | 3.38E-03 |
| Cellular response to topologically incorrect protein | 6/120 genes, 5.0% | 44/3521 genes, 1.2% | 3.38E-03 |
| Regulation of macrophage activation | 2/120 genes, 1.7% | 3/3521 genes, 0.1% | 3.38E-03 |
| Cellular response to extracellular stimulus | 5/120 genes, 4.2% | 31/3521 genes, 0.9% | 3.53E-03 |
| 'De novo' protein folding | 6/120 genes, 5.0% | 45/3521 genes, 1.3% | 3.79E-03 |
| Generation of precursor metabolites and energy | 14/120 genes, 11.7% | 188/3521 genes, 5.3% | 4.21E-03 |
| Response to extracellular stimulus | 8/120 genes, 6.7% | 78/3521 genes, 2.2% | 4.58E-03 |
| Keratinocyte differentiation | 4/120 genes, 3.3% | 21/3521 genes, 0.6% | 4.90E-03 |
| Cellular component disassembly | 10/120 genes, 8.3% | 114/3521 genes, 3.2% | 4.94E-03 |
| Positive regulation of nuclease activity | 5/120 genes, 4.2% | 34/3521 genes, 1.0% | 5.33E-03 |

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|------------------------------------------------|--|----------------------|------------------------|----------|
| Response to endoplasmic reticulum stress | | 6/120 genes, 5.0% | 49/3521 genes, 1.4% | 5.83E-03 |
| Fructose 1,6-bisphosphate metabolic process | | 2/120 genes, 1.7% | 4/3521 genes, 0.1% | 6.61E-03 |
| Intermediate filament organization | | 2/120 genes, 1.7% | 4/3521 genes, 0.1% | 6.61E-03 |
| Regulation of cell aging | | 2/120 genes, 1.7% | 4/3521 genes, 0.1% | 6.61E-03 |
| Ribosome biogenesis | | 9/120 genes, 7.5% | 102/3521 genes, 2.9% | 7.30E-03 |
| Single-organism carbohydrate metabolic process | | 13/120 genes, 10.8% | 181/3521 genes, 5.1% | 7.84E-03 |
| Epidermal cell differentiation | | 4/120 genes, 3.3% | 24/3521 genes, 0.7% | 8.04E-03 |
| Cell differentiation | | 26/120 genes, 21.7% | 478/3521 genes, 13.6% | 8.88E-03 |
| DNA-dependent DNA replication | | 5/120 genes, 4.2% | 39/3521 genes, 1.1% | 9.63E-03 |
| Single-multicellular organism process | | 45/120 genes, 37.5% | 972/3521 genes, 27.6% | 1.05E-02 |
| DNA duplex unwinding | | 3/120 genes, 2.5% | 14/3521 genes, 0.4% | 1.07E-02 |
| G1/S transition of mitotic cell cycle | | 5/120 genes, 4.2% | 40/3521 genes, 1.1% | 1.07E-02 |
| 'De novo' posttranslational protein folding | | 5/120 genes, 4.2% | 40/3521 genes, 1.1% | 1.07E-02 |
| Chaperone-mediated protein folding | | 4/120 genes, 3.3% | 26/3521 genes, 0.7% | 1.07E-02 |
| Peptide cross-linking | | 2/120 genes, 1.7% | 5/3521 genes, 0.1% | 1.08E-02 |
| Cellular component organization or biogenesis | | 55/120 genes, 45.8% | 1248/3521 genes, 35.4% | 1.09E-02 |
| Response to organic cyclic compound | | 11/120 genes, 9.2% | 148/3521 genes, 4.2% | 1.11E-02 |
| Cellular process | | 114/120 genes, 95.0% | 3118/3521 genes, 88.6% | 1.14E-02 |
| Establishment or maintenance of cell polarity | | 5/120 genes, 4.2% | 41/3521 genes, 1.2% | 1.19E-02 |
| Regeneration | | 4/120 genes, 3.3% | 27/3521 genes, 0.8% | 1.23E-02 |
| Chromosome condensation | | 3/120 genes, 2.5% | 15/3521 genes, 0.4% | 1.30E-02 |
| DNA geometric change | | 3/120 genes, 2.5% | 15/3521 genes, 0.4% | 1.30E-02 |
| Single-organism developmental process | | 32/120 genes, 26.7% | 644/3521 genes, 18.3% | 1.35E-02 |
| Multicellular organismal process | | 46/120 genes, 38.3% | 1013/3521 genes, 28.8% | 1.37E-02 |

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|------------------------------------------------------------------------------|---------------------|------------------------|----------|
| Cellular developmental process | 26/120 genes, 21.7% | 495/3521 genes, 14.1% | 1.38E-02 |
| Cellular component disassembly involved in execution phase of apoptosis | 5/120 genes, 4.2% | 43/3521 genes, 1.2% | 1.45E-02 |
| Execution phase of apoptosis | 5/120 genes, 4.2% | 43/3521 genes, 1.2% | 1.45E-02 |
| Extracellular matrix organization | 4/120 genes, 3.3% | 29/3521 genes, 0.8% | 1.58E-02 |
| Extracellular structure organization | 4/120 genes, 3.3% | 29/3521 genes, 0.8% | 1.58E-02 |
| Fructose metabolic process | 2/120 genes, 1.7% | 6/3521 genes, 0.2% | 1.58E-02 |
| Regulation of DNA damage response, signal transduction by p53 class mediator | 2/120 genes, 1.7% | 6/3521 genes, 0.2% | 1.58E-02 |
| Regulation of signal transduction by p53 class mediator | 2/120 genes, 1.7% | 6/3521 genes, 0.2% | 1.58E-02 |
| Regulation of apoptotic process | 18/120 genes, 15.0% | 310/3521 genes, 8.8% | 1.62E-02 |
| Carbohydrate metabolic process | 15/120 genes, 12.5% | 243/3521 genes, 6.9% | 1.67E-02 |
| Regulation of programmed cell death | 18/120 genes, 15.0% | 314/3521 genes, 8.9% | 1.83E-02 |
| Cellular response to organic cyclic compound | 5/120 genes, 4.2% | 46/3521 genes, 1.3% | 1.90E-02 |
| Cellular response to external stimulus | 5/120 genes, 4.2% | 46/3521 genes, 1.3% | 1.90E-02 |
| Ribonucleoprotein complex biogenesis | 11/120 genes, 9.2% | 160/3521 genes, 4.5% | 1.92E-02 |
| Single-organism process | 92/120 genes, 76.7% | 2385/3521 genes, 67.7% | 1.92E-02 |
| Male sex differentiation | 4/120 genes, 3.3% | 31/3521 genes, 0.9% | 1.98E-02 |
| Intermediate filament-based process | 2/120 genes, 1.7% | 7/3521 genes, 0.2% | 2.16E-02 |
| Intermediate filament cytoskeleton organization | 2/120 genes, 1.7% | 7/3521 genes, 0.2% | 2.16E-02 |
| Mitochondrion localization | 2/120 genes, 1.7% | 7/3521 genes, 0.2% | 2.16E-02 |
| Mitotic sister chromatid segregation | 3/120 genes, 2.5% | 18/3521 genes, 0.5% | 2.17E-02 |
| Regulation of protein secretion | 3/120 genes, 2.5% | 18/3521 genes, 0.5% | 2.17E-02 |

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|--------------------------------------------------------------------------------|---------------------|------------------------|----------|
| Activation of signaling protein activity involved in unfolded protein response | 4/120 genes, 3.3% | 32/3521 genes, 0.9% | 2.21E-02 |
| Negative regulation of neuron apoptotic process | 4/120 genes, 3.3% | 32/3521 genes, 0.9% | 2.21E-02 |
| Negative regulation of neuron death | 4/120 genes, 3.3% | 32/3521 genes, 0.9% | 2.21E-02 |
| Response to external stimulus | 14/120 genes, 11.7% | 230/3521 genes, 6.5% | 2.30E-02 |
| Viral reproductive process | 14/120 genes, 11.7% | 230/3521 genes, 6.5% | 2.30E-02 |
| Epidermis development | 5/120 genes, 4.2% | 49/3521 genes, 1.4% | 2.44E-02 |
| Regulation of cell death | 18/120 genes, 15.0% | 324/3521 genes, 9.2% | 2.44E-02 |
| Nucleosome organization | 4/120 genes, 3.3% | 33/3521 genes, 0.9% | 2.45E-02 |
| Nervous system development | 19/120 genes, 15.8% | 349/3521 genes, 9.9% | 2.53E-02 |
| Cellular response to stress | 20/120 genes, 16.7% | 374/3521 genes, 10.6% | 2.59E-02 |
| Chromatin assembly or disassembly | 4/120 genes, 3.3% | 34/3521 genes, 1.0% | 2.70E-02 |
| ATP catabolic process | 6/120 genes, 5.0% | 68/3521 genes, 1.9% | 2.70E-02 |
| Translational elongation | 6/120 genes, 5.0% | 68/3521 genes, 1.9% | 2.70E-02 |
| Organic anion transport | 5/120 genes, 4.2% | 51/3521 genes, 1.4% | 2.84E-02 |
| Sister chromatid segregation | 3/120 genes, 2.5% | 20/3521 genes, 0.6% | 2.88E-02 |
| ATP metabolic process | 7/120 genes, 5.8% | 88/3521 genes, 2.5% | 2.91E-02 |
| Rhythmic process | 4/120 genes, 3.3% | 35/3521 genes, 1.0% | 2.97E-02 |
| Small molecule metabolic process | 39/120 genes, 32.5% | 870/3521 genes, 24.7% | 3.09E-02 |
| Response to inorganic substance | 8/120 genes, 6.7% | 109/3521 genes, 3.1% | 3.10E-02 |
| Negative regulation of apoptotic process | 8/120 genes, 6.7% | 109/3521 genes, 3.1% | 3.10E-02 |
| Primary metabolic process | 85/120 genes, 70.8% | 2199/3521 genes, 62.5% | 3.19E-02 |
| Cellular aldehyde metabolic process | 3/120 genes, 2.5% | 21/3521 genes, 0.6% | 3.28E-02 |
| Cellular response to starvation | 3/120 genes, 2.5% | 21/3521 genes, 0.6% | 3.28E-02 |
| Epithelial cell differentiation | 5/120 genes, 4.2% | 53/3521 genes, 1.5% | 3.29E-02 |
| Single-organism behavior | 5/120 genes, 4.2% | 53/3521 genes, 1.5% | 3.29E-02 |
| Cellular component organization | 50/120 genes, 41.7% | 1178/3521 genes, 33.5% | 3.43E-02 |
| Response to nutrient levels | 6/120 genes, 5.0% | 72/3521 genes, 2.0% | 3.46E-02 |
| Neurogenesis | 14/120 genes, 11.7% | 243/3521 genes, 6.9% | 3.49E-02 |

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| Sister chromatid cohesion | 2/120 genes, 1.7% | 9/3521 genes, 0.3% | 3.55E-02 |
| Purine nucleobase biosynthetic process | 2/120 genes, 1.7% | 9/3521 genes, 0.3% | 3.55E-02 |
| Protein refolding | 2/120 genes, 1.7% | 9/3521 genes, 0.3% | 3.55E-02 |
| Ribosomal large subunit biogenesis | 2/120 genes, 1.7% | 9/3521 genes, 0.3% | 3.55E-02 |
| Negative regulation of programmed cell death | 8/120 genes, 6.7% | 112/3521 genes, 3.2% | 3.56E-02 |
| Ribonucleotide metabolic process | 13/120 genes, 10.8% | 222/3521 genes, 6.3% | 3.70E-02 |
| Sensory perception of sound | 3/120 genes, 2.5% | 22/3521 genes, 0.6% | 3.71E-02 |
| Cell communication | 37/120 genes, 30.8% | 828/3521 genes, 23.5% | 3.77E-02 |
| Protein-DNA complex subunit organization | 4/120 genes, 3.3% | 38/3521 genes, 1.1% | 3.88E-02 |
| Ovulation cycle process | 3/120 genes, 2.5% | 23/3521 genes, 0.7% | 4.16E-02 |
| Ovulation cycle | 3/120 genes, 2.5% | 23/3521 genes, 0.7% | 4.16E-02 |
| Organic substance metabolic process | 86/120 genes, 71.7% | 2249/3521 genes, 63.9% | 4.17E-02 |
| Ribose phosphate metabolic process | 13/120 genes, 10.8% | 226/3521 genes, 6.4% | 4.19E-02 |
| Gonad development | 4/120 genes, 3.3% | 39/3521 genes, 1.1% | 4.21E-02 |
| Response to cadmium ion | 2/120 genes, 1.7% | 10/3521 genes, 0.3% | 4.33E-02 |
| Neuromuscular process controlling balance | 2/120 genes, 1.7% | 10/3521 genes, 0.3% | 4.33E-02 |
| Organ development | 21/120 genes, 17.5% | 421/3521 genes, 12.0% | 4.42E-02 |
| Nucleosome assembly | 3/120 genes, 2.5% | 24/3521 genes, 0.7% | 4.64E-02 |
| Sensory perception of mechanical stimulus | 3/120 genes, 2.5% | 24/3521 genes, 0.7% | 4.64E-02 |
| Cell death | 14/120 genes, 11.7% | 254/3521 genes, 7.2% | 4.80E-02 |
| Death | 14/120 genes, 11.7% | 254/3521 genes, 7.2% | 4.80E-02 |
| Apoptotic process | 12/120 genes, 10.0% | 208/3521 genes, 5.9% | 4.88E-02 |
| Dicarboxylic acid metabolic process | 4/120 genes, 3.3% | 41/3521 genes, 1.2% | 4.92E-02 |
| Single-organism cellular process | 84/120 genes, 70.0% | 2200/3521 genes, 62.5% | 4.95E-02 |

Supplementary Table S12. Gene ontology enrichment between BSN group and Control group (component ontology) ($P < 0.05$).

| Gene ontology term | Cluster frequency | Protein frequency of use | <i>P</i> value |
|----------------------------------------------|---------------------|--------------------------|----------------|
| Extracellular organelle | 2/29 genes, 6.9% | 5/3725 genes, 0.1% | 5.77E-04 |
| Extracellular membrane-bounded organelle | 2/29 genes, 6.9% | 5/3725 genes, 0.1% | 5.77E-04 |
| Extracellular vesicular exosome | 2/29 genes, 6.9% | 5/3725 genes, 0.1% | 5.77E-04 |
| Cytoplasm | 29/29 genes, 100.0% | 2929/3725 genes, 78.6% | 9.10E-04 |
| Melanosome | 4/29 genes, 13.8% | 64/3725 genes, 1.7% | 1.36E-03 |
| Pigment granule | 4/29 genes, 13.8% | 64/3725 genes, 1.7% | 1.36E-03 |
| Macromolecular complex | 20/29 genes, 69.0% | 1533/3725 genes, 41.2% | 2.22E-03 |
| Nuclear chromosome part | 4/29 genes, 13.8% | 83/3725 genes, 2.2% | 3.56E-03 |
| Cell surface | 4/29 genes, 13.8% | 86/3725 genes, 2.3% | 4.05E-03 |
| Nuclear replication fork | 2/29 genes, 6.9% | 16/3725 genes, 0.4% | 6.56E-03 |
| Nuclear chromosome | 4/29 genes, 13.8% | 101/3725 genes, 2.7% | 7.18E-03 |
| Protein complex | 16/29 genes, 55.2% | 1219/3725 genes, 32.7% | 1.02E-02 |
| Extracellular region part | 4/29 genes, 13.8% | 115/3725 genes, 3.1% | 1.13E-02 |
| Nucleolus | 10/29 genes, 34.5% | 639/3725 genes, 17.2% | 1.83E-02 |
| Chromosomal part | 5/29 genes, 17.2% | 203/3725 genes, 5.4% | 1.86E-02 |
| Replication fork | 2/29 genes, 6.9% | 28/3725 genes, 0.8% | 1.95E-02 |
| Coated pit | 2/29 genes, 6.9% | 28/3725 genes, 0.8% | 1.95E-02 |
| Ribonucleoprotein complex | 7/29 genes, 24.1% | 369/3725 genes, 9.9% | 2.02E-02 |
| Cell projection | 6/29 genes, 20.7% | 295/3725 genes, 7.9% | 2.35E-02 |
| Non-membrane-bounded organelle | 16/29 genes, 55.2% | 1324/3725 genes, 35.5% | 2.36E-02 |
| Intracellular non-membrane-bounded organelle | 16/29 genes, 55.2% | 1324/3725 genes, 35.5% | 2.36E-02 |
| Chromosome | 5/29 genes, 17.2% | 235/3725 genes, 6.3% | 3.27E-02 |
| Cytoskeleton | 8/29 genes, 27.6% | 507/3725 genes, 13.6% | 3.51E-02 |
| Cell projection membrane | 2/29 genes, 6.9% | 42/3725 genes, 1.1% | 4.16E-02 |
| Cytosol | 13/29 genes, 44.8% | 1066/3725 genes, 28.6% | 4.55E-02 |
| Nuclear periphery | 2/29 genes, 6.9% | 46/3725 genes, 1.2% | 4.90E-02 |

Supplementary Table S13. Gene ontology enrichment between BSN group and Control group (function ontology) ($P < 0.05$).

| Gene ontology term | Cluster frequency | Protein frequency of use | <i>P</i> value |
|-------------------------------------------------------------------------------------------------------|--------------------|--------------------------|----------------|
| Unfolded protein binding | 4/28 genes, 14.3% | 72/3499 genes, 2.1% | 2.32E-03 |
| Ion channel binding | 2/28 genes, 7.1% | 13/3499 genes, 0.4% | 4.56E-03 |
| Translation elongation factor activity | 2/28 genes, 7.1% | 22/3499 genes, 0.6% | 1.29E-02 |
| Translation factor activity, nucleic acid binding | 3/28 genes, 10.7% | 73/3499 genes, 2.1% | 1.96E-02 |
| Heterocyclic compound binding | 18/28 genes, 64.3% | 1513/3499 genes, 43.2% | 1.98E-02 |
| Chaperone binding | 2/28 genes, 7.1% | 28/3499 genes, 0.8% | 2.05E-02 |
| Organic cyclic compound binding | 18/28 genes, 64.3% | 1519/3499 genes, 43.4% | 2.07E-02 |
| Structure-specific DNA binding | 3/28 genes, 10.7% | 78/3499 genes, 2.2% | 2.34E-02 |
| Purine ribonucleoside triphosphate binding | 10/28 genes, 35.7% | 651/3499 genes, 18.6% | 2.42E-02 |
| Purine ribonucleoside binding | 10/28 genes, 35.7% | 652/3499 genes, 18.6% | 2.44E-02 |
| Purine nucleoside binding | 10/28 genes, 35.7% | 653/3499 genes, 18.7% | 2.47E-02 |
| Ribonucleoside binding | 10/28 genes, 35.7% | 654/3499 genes, 18.7% | 2.49E-02 |
| Purine ribonucleotide binding | 10/28 genes, 35.7% | 654/3499 genes, 18.7% | 2.49E-02 |
| Nucleoside binding | 10/28 genes, 35.7% | 657/3499 genes, 18.8% | 2.57E-02 |
| Purine nucleotide binding | 10/28 genes, 35.7% | 659/3499 genes, 18.8% | 2.62E-02 |
| Ribonucleotide binding | 10/28 genes, 35.7% | 659/3499 genes, 18.8% | 2.62E-02 |
| RNA binding | 8/28 genes, 28.6% | 472/3499 genes, 13.5% | 2.73E-02 |
| GTP binding | 4/28 genes, 14.3% | 148/3499 genes, 4.2% | 2.85E-02 |
| Guanyl nucleotide binding | 4/28 genes, 14.3% | 149/3499 genes, 4.3% | 2.92E-02 |
| Guanyl ribonucleotide binding | 4/28 genes, 14.3% | 149/3499 genes, 4.3% | 2.92E-02 |
| Nucleoside-triphosphatase activity | 6/28 genes, 21.4% | 323/3499 genes, 9.2% | 3.89E-02 |
| ATPase activity | 4/28 genes, 14.3% | 165/3499 genes, 4.7% | 4.03E-02 |
| Oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen | 2/28 genes, 7.1% | 41/3499 genes, 1.2% | 4.18E-02 |
| Receptor binding | 5/28 genes, 17.9% | 245/3499 genes, 7.0% | 4.21E-02 |
| Pyrophosphatase activity | 6/28 genes, 21.4% | 331/3499 genes, 9.5% | 4.31E-02 |
| Hydrolase activity, acting on acid anhydrides | 6/28 genes, 21.4% | 331/3499 genes, 9.5% | 4.31E-02 |
| Hydrolase activity, acting on acid anhydrides, in phosphorus-containing | 6/28 genes, 21.4% | 331/3499 genes, 9.5% | 4.31E-02 |

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| ATP binding | 8/28 genes, 28.6% | 517/3499 genes, 14.8% | 4.43E-02 |
| Anion binding | 11/28 genes, 39.3% | 823/3499 genes, 23.5% | 4.53E-02 |
| Single-stranded DNA binding | 2/28 genes, 7.1% | 43/3499 genes, 1.2% | 4.56E-02 |
| Nucleic acid binding | 11/28 genes, 39.3% | 824/3499 genes, 23.5% | 4.56E-02 |
| Adenyl ribonucleotide binding | 8/28 genes, 28.6% | 521/3499 genes, 14.9% | 4.61E-02 |
| Adenyl nucleotide binding | 8/28 genes, 28.6% | 524/3499 genes, 15.0% | 4.75E-02 |
| Protein binding | 23/28 genes, 82.1% | 2312/3499 genes, 66.1% | 4.95E-02 |

Supplementary Table S14. Gene ontology enrichment between BSN group and Control group (process ontology) ($P < 0.05$).

| Gene ontology term | Cluster frequency | Protein frequency of use | <i>P</i> value |
|------------------------------------------------------|--------------------|--------------------------|----------------|
| Chaperone-mediated protein complex assembly | 2/29 genes, 6.9% | 5/3521 genes, 0.1% | 6.45E-04 |
| System development | 13/29 genes, 44.8% | 647/3521 genes, 18.4% | 9.05E-04 |
| Ribonucleoside triphosphate catabolic process | 6/29 genes, 20.7% | 163/3521 genes, 4.6% | 1.75E-03 |
| Purine ribonucleoside triphosphate catabolic process | 6/29 genes, 20.7% | 163/3521 genes, 4.6% | 1.75E-03 |
| DNA recombination | 4/29 genes, 13.8% | 65/3521 genes, 1.8% | 1.78E-03 |
| Purine nucleoside triphosphate catabolic process | 6/29 genes, 20.7% | 164/3521 genes, 4.7% | 1.81E-03 |
| Nucleoside triphosphate catabolic process | 6/29 genes, 20.7% | 165/3521 genes, 4.7% | 1.87E-03 |
| Purine ribonucleotide catabolic process | 6/29 genes, 20.7% | 166/3521 genes, 4.7% | 1.93E-03 |
| Ribonucleotide catabolic process | 6/29 genes, 20.7% | 166/3521 genes, 4.7% | 1.93E-03 |
| Purine nucleoside catabolic process | 6/29 genes, 20.7% | 167/3521 genes, 4.7% | 1.99E-03 |
| Purine ribonucleoside catabolic process | 6/29 genes, 20.7% | 167/3521 genes, 4.7% | 1.99E-03 |
| ATP catabolic process | 4/29 genes, 13.8% | 68/3521 genes, 1.9% | 2.10E-03 |
| Ribonucleoside catabolic process | 6/29 genes, 20.7% | 169/3521 genes, 4.8% | 2.11E-03 |
| Nucleoside catabolic process | 6/29 genes, 20.7% | 174/3521 genes, 4.9% | 2.45E-03 |
| Multicellular organismal process | 16/29 genes, 55.2% | 1013/3521 genes, 28.8% | 2.47E-03 |
| Purine nucleotide catabolic process | 6/29 genes, 20.7% | 175/3521 genes, 5.0% | 2.52E-03 |
| Purine-containing compound catabolic process | 6/29 genes, 20.7% | 176/3521 genes, 5.0% | 2.60E-03 |
| Glycosyl compound catabolic process | 6/29 genes, 20.7% | 177/3521 genes, 5.0% | 2.67E-03 |
| Nucleotide catabolic process | 6/29 genes, 20.7% | 180/3521 genes, 5.1% | 2.91E-03 |
| Regulation of intracellular transport | 4/29 genes, 13.8% | 76/3521 genes, 2.2% | 3.16E-03 |
| Nucleoside phosphate catabolic process | 6/29 genes, 20.7% | 183/3521 genes, 5.2% | 3.16E-03 |

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| Purine ribonucleoside triphosphate metabolic process | 6/29 genes, 20.7% | 186/3521 genes, 5.3% | 3.43E-03 |
| Purine nucleoside triphosphate metabolic process | 6/29 genes, 20.7% | 189/3521 genes, 5.4% | 3.72E-03 |
| Ribonucleoside triphosphate metabolic process | 6/29 genes, 20.7% | 189/3521 genes, 5.4% | 3.72E-03 |
| Organophosphate catabolic process | 6/29 genes, 20.7% | 190/3521 genes, 5.4% | 3.82E-03 |
| Nucleobase-containing compound catabolic process | 8/29 genes, 27.6% | 330/3521 genes, 9.4% | 4.04E-03 |
| Multicellular organismal development | 13/29 genes, 44.8% | 764/3521 genes, 21.7% | 4.42E-03 |
| Nucleoside triphosphate metabolic process | 6/29 genes, 20.7% | 196/3521 genes, 5.6% | 4.46E-03 |
| Anatomical structure development | 13/29 genes, 44.8% | 769/3521 genes, 21.8% | 4.70E-03 |
| Nucleotide-excision repair, DNA gap filling | 2/29 genes, 6.9% | 13/3521 genes, 0.4% | 4.83E-03 |
| Single-multicellular organism process | 15/29 genes, 51.7% | 972/3521 genes, 27.6% | 4.91E-03 |
| Carbohydrate derivative catabolic process | 6/29 genes, 20.7% | 201/3521 genes, 5.7% | 5.05E-03 |
| Heterocycle catabolic process | 8/29 genes, 27.6% | 343/3521 genes, 9.7% | 5.13E-03 |
| Aromatic compound catabolic process | 8/29 genes, 27.6% | 344/3521 genes, 9.8% | 5.23E-03 |
| Cellular nitrogen compound catabolic process | 8/29 genes, 27.6% | 344/3521 genes, 9.8% | 5.23E-03 |
| ATP metabolic process | 4/29 genes, 13.8% | 88/3521 genes, 2.5% | 5.37E-03 |
| 'De novo' protein folding | 3/29 genes, 10.3% | 45/3521 genes, 1.3% | 5.65E-03 |
| Organic cyclic compound catabolic process | 8/29 genes, 27.6% | 352/3521 genes, 10.0% | 6.01E-03 |
| Purine ribonucleotide metabolic process | 6/29 genes, 20.7% | 214/3521 genes, 6.1% | 6.86E-03 |
| Purine ribonucleoside metabolic process | 6/29 genes, 20.7% | 214/3521 genes, 6.1% | 6.86E-03 |
| Purine nucleoside metabolic process | 6/29 genes, 20.7% | 215/3521 genes, 6.1% | 7.01E-03 |
| Telomere maintenance via semi-conservative replication | 2/29 genes, 6.9% | 16/3521 genes, 0.5% | 7.32E-03 |
| Regulation of intracellular protein transport | 3/29 genes, 10.3% | 50/3521 genes, 1.4% | 7.59E-03 |
| Catabolic process | 12/29 genes, 41.4% | 716/3521 genes, 20.3% | 7.72E-03 |

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|---------------------------------------------------|--------------------|------------------------|----------|
| Regulation of nucleocytoplasmic transport | 3/29 genes, 10.3% | 51/3521 genes, 1.4% | 8.02E-03 |
| Ribonucleotide metabolic process | 6/29 genes, 20.7% | 222/3521 genes, 6.3% | 8.18E-03 |
| Telomere maintenance via recombination | 2/29 genes, 6.9% | 17/3521 genes, 0.5% | 8.25E-03 |
| Cellular catabolic process | 11/29 genes, 37.9% | 634/3521 genes, 18.0% | 8.84E-03 |
| Ribonucleoside metabolic process | 6/29 genes, 20.7% | 226/3521 genes, 6.4% | 8.91E-03 |
| Ribose phosphate metabolic process | 6/29 genes, 20.7% | 226/3521 genes, 6.4% | 8.91E-03 |
| Purine nucleotide metabolic process | 6/29 genes, 20.7% | 227/3521 genes, 6.4% | 9.10E-03 |
| Mitotic recombination | 2/29 genes, 6.9% | 19/3521 genes, 0.5% | 1.03E-02 |
| Cholesterol biosynthetic process | 2/29 genes, 6.9% | 19/3521 genes, 0.5% | 1.03E-02 |
| Nucleoside metabolic process | 6/29 genes, 20.7% | 237/3521 genes, 6.7% | 1.12E-02 |
| Purine-containing compound metabolic process | 6/29 genes, 20.7% | 241/3521 genes, 6.8% | 1.21E-02 |
| Telomere maintenance via telomere lengthening | 2/29 genes, 6.9% | 21/3521 genes, 0.6% | 1.25E-02 |
| Glycosyl compound metabolic process | 6/29 genes, 20.7% | 243/3521 genes, 6.9% | 1.25E-02 |
| Cellular component organization | 16/29 genes, 55.2% | 1178/3521 genes, 33.5% | 1.28E-02 |
| Developmental process | 13/29 genes, 44.8% | 863/3521 genes, 24.5% | 1.30E-02 |
| Virus-host interaction | 5/29 genes, 17.2% | 176/3521 genes, 5.0% | 1.32E-02 |
| Lymphocyte mediated immunity | 2/29 genes, 6.9% | 22/3521 genes, 0.6% | 1.37E-02 |
| Sterol biosynthetic process | 2/29 genes, 6.9% | 22/3521 genes, 0.6% | 1.37E-02 |
| Response to unfolded protein | 3/29 genes, 10.3% | 62/3521 genes, 1.8% | 1.37E-02 |
| Cellular macromolecular complex assembly | 5/29 genes, 17.2% | 181/3521 genes, 5.1% | 1.47E-02 |
| Organophosphate metabolic process | 8/29 genes, 27.6% | 410/3521 genes, 11.6% | 1.48E-02 |
| Organic substance catabolic process | 11/29 genes, 37.9% | 683/3521 genes, 19.4% | 1.54E-02 |
| Response to topologically incorrect protein | 3/29 genes, 10.3% | 65/3521 genes, 1.8% | 1.56E-02 |
| DNA strand elongation involved in DNA replication | 2/29 genes, 6.9% | 24/3521 genes, 0.7% | 1.62E-02 |
| DNA strand elongation | 2/29 genes, 6.9% | 24/3521 genes, 0.7% | 1.62E-02 |
| Interaction with host | 5/29 genes, 17.2% | 189/3521 genes, 5.4% | 1.75E-02 |
| Translational elongation | 3/29 genes, 10.3% | 68/3521 genes, 1.9% | 1.76E-02 |

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|------------------------------------------------------|--------------------|------------------------|----------|
| Symbiosis, encompassing mutualism through parasitism | 5/29 genes, 17.2% | 192/3521 genes, 5.5% | 1.86E-02 |
| Interspecies interaction between organisms | 5/29 genes, 17.2% | 192/3521 genes, 5.5% | 1.86E-02 |
| Transcription-coupled nucleotide-excision repair | 2/29 genes, 6.9% | 26/3521 genes, 0.7% | 1.88E-02 |
| Chaperone-mediated protein folding | 2/29 genes, 6.9% | 26/3521 genes, 0.7% | 1.88E-02 |
| Protein folding | 4/29 genes, 13.8% | 127/3521 genes, 3.6% | 1.91E-02 |
| Macromolecular complex assembly | 7/29 genes, 24.1% | 348/3521 genes, 9.9% | 1.99E-02 |
| Organic cyclic compound metabolic process | 16/29 genes, 55.2% | 1231/3521 genes, 35.0% | 2.00E-02 |
| Organonitrogen compound catabolic process | 6/29 genes, 20.7% | 271/3521 genes, 7.7% | 2.07E-02 |
| Reproduction | 8/29 genes, 27.6% | 436/3521 genes, 12.4% | 2.10E-02 |
| Regulation of protein transport | 3/29 genes, 10.3% | 73/3521 genes, 2.1% | 2.12E-02 |
| Cellular component organization or biogenesis | 16/29 genes, 55.2% | 1248/3521 genes, 35.4% | 2.29E-02 |
| Cellular component assembly | 8/29 genes, 27.6% | 443/3521 genes, 12.6% | 2.29E-02 |
| Leukocyte mediated immunity | 2/29 genes, 6.9% | 29/3521 genes, 0.8% | 2.32E-02 |
| Protein-DNA complex assembly | 2/29 genes, 6.9% | 29/3521 genes, 0.8% | 2.32E-02 |
| Response to stress | 11/29 genes, 37.9% | 724/3521 genes, 20.6% | 2.35E-02 |
| Translation | 5/29 genes, 17.2% | 204/3521 genes, 5.8% | 2.36E-02 |
| Response to chemical stimulus | 11/29 genes, 37.9% | 725/3521 genes, 20.6% | 2.37E-02 |
| Cellular component biogenesis | 9/29 genes, 31.0% | 536/3521 genes, 15.2% | 2.39E-02 |
| Telomere maintenance | 2/29 genes, 6.9% | 31/3521 genes, 0.9% | 2.63E-02 |
| Telomere organization | 2/29 genes, 6.9% | 31/3521 genes, 0.9% | 2.63E-02 |
| Regulation of microtubule-based process | 2/29 genes, 6.9% | 31/3521 genes, 0.9% | 2.63E-02 |
| Cellular protein complex assembly | 3/29 genes, 10.3% | 80/3521 genes, 2.3% | 2.70E-02 |
| Macromolecular complex subunit organization | 8/29 genes, 27.6% | 459/3521 genes, 13.0% | 2.78E-02 |
| S phase of mitotic cell cycle | 3/29 genes, 10.3% | 81/3521 genes, 2.3% | 2.79E-02 |
| S phase | 3/29 genes, 10.3% | 82/3521 genes, 2.3% | 2.88E-02 |
| Homeostasis of number of cells | 2/29 genes, 6.9% | 33/3521 genes, 0.9% | 2.95E-02 |
| Regulation of establishment of protein localization | 3/29 genes, 10.3% | 84/3521 genes, 2.4% | 3.06E-02 |

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|--------------------------------------------------|--------------------|------------------------|----------|
| M phase | 4/29 genes, 13.8% | 147/3521 genes, 4.2% | 3.07E-02 |
| Nucleotide-excision repair | 2/29 genes, 6.9% | 34/3521 genes, 1.0% | 3.12E-02 |
| Meiosis | 2/29 genes, 6.9% | 34/3521 genes, 1.0% | 3.12E-02 |
| Alcohol biosynthetic process | 2/29 genes, 6.9% | 34/3521 genes, 1.0% | 3.12E-02 |
| M phase of meiotic cell cycle | 2/29 genes, 6.9% | 34/3521 genes, 1.0% | 3.12E-02 |
| Immune system development | 3/29 genes, 10.3% | 85/3521 genes, 2.4% | 3.16E-02 |
| Viral reproduction | 6/29 genes, 20.7% | 300/3521 genes, 8.5% | 3.23E-02 |
| Multi-organism cellular process | 6/29 genes, 20.7% | 301/3521 genes, 8.5% | 3.28E-02 |
| Steroid biosynthetic process | 2/29 genes, 6.9% | 35/3521 genes, 1.0% | 3.30E-02 |
| Cholesterol metabolic process | 2/29 genes, 6.9% | 35/3521 genes, 1.0% | 3.30E-02 |
| Axon guidance | 3/29 genes, 10.3% | 88/3521 genes, 2.5% | 3.45E-02 |
| Regulation of protein import into nucleus | 2/29 genes, 6.9% | 36/3521 genes, 1.0% | 3.47E-02 |
| Regulation of protein localization to nucleus | 2/29 genes, 6.9% | 36/3521 genes, 1.0% | 3.47E-02 |
| Nucleotide metabolic process | 6/29 genes, 20.7% | 307/3521 genes, 8.7% | 3.57E-02 |
| Carbohydrate derivative metabolic process | 7/29 genes, 24.1% | 392/3521 genes, 11.1% | 3.58E-02 |
| Nucleoside phosphate metabolic process | 6/29 genes, 20.7% | 308/3521 genes, 8.7% | 3.62E-02 |
| Meiotic cell cycle | 2/29 genes, 6.9% | 37/3521 genes, 1.1% | 3.65E-02 |
| Organic hydroxy compound biosynthetic process | 2/29 genes, 6.9% | 37/3521 genes, 1.1% | 3.65E-02 |
| Viral reproductive process | 5/29 genes, 17.2% | 230/3521 genes, 6.5% | 3.73E-02 |
| Sterol metabolic process | 2/29 genes, 6.9% | 38/3521 genes, 1.1% | 3.83E-02 |
| Protein-DNA complex subunit organization | 2/29 genes, 6.9% | 38/3521 genes, 1.1% | 3.83E-02 |
| DNA-dependent DNA replication | 2/29 genes, 6.9% | 39/3521 genes, 1.1% | 4.02E-02 |
| G1/S transition of mitotic cell cycle | 2/29 genes, 6.9% | 40/3521 genes, 1.1% | 4.21E-02 |
| Regulation of homeostatic process | 2/29 genes, 6.9% | 40/3521 genes, 1.1% | 4.21E-02 |
| 'De novo' posttranslational protein folding | 2/29 genes, 6.9% | 40/3521 genes, 1.1% | 4.21E-02 |
| Regulation of protein localization | 3/29 genes, 10.3% | 98/3521 genes, 2.8% | 4.53E-02 |
| Regulation of cellular localization | 4/29 genes, 13.8% | 168/3521 genes, 4.8% | 4.68E-02 |
| Nucleobase-containing compound metabolic process | 14/29 genes, 48.3% | 1122/3521 genes, 31.9% | 4.73E-02 |
| Cell cycle phase | 5/29 genes, 17.2% | 247/3521 genes, 7.0% | 4.84E-02 |

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|--------------------------------------------------------|-------------------|----------------------|----------|
| Nucleobase-containing small molecule metabolic process | 6/29 genes, 20.7% | 332/3521 genes, 9.4% | 4.96E-02 |
| Protein complex assembly | 5/29 genes, 17.2% | 249/3521 genes, 7.1% | 4.98E-02 |

Supplementary Table S15. Kyoto encyclopedia of genes and genomes enrichment between E@TSN group and Control group ($P < 0.05$).

| Pathway ID | Pathway | Diff Proteins with pathway annotation (170) | All Proteins with pathway annotation (3333) | <i>P</i> value |
|------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|----------------|
| ko04612 | Antigen processing and presentation | 7 (4.12%) | 27 (0.81%) | 3.00E-04 |
| ko03013 | RNA transport | 15 (8.82%) | 130 (3.9%) | 2.17E-03 |
| ko03010 | Ribosome | 8 (4.71%) | 58 (1.74%) | 8.36E-03 |
| ko04141 | Protein processing in endoplasmic reticulum | 12 (7.06%) | 117 (3.51%) | 1.49E-02 |
| ko00010 | Glycolysis / Gluconeogenesis | 6 (3.53%) | 42 (1.26%) | 1.83E-02 |
| ko05322 | Systemic lupus erythematosus | 4 (2.35%) | 21 (0.63%) | 1.98E-02 |
| ko03040 | Spliceosome | 12 (7.06%) | 127 (3.81%) | 2.68E-02 |
| ko03030 | DNA replication | 4 (2.35%) | 25 (0.75%) | 3.57E-02 |
| ko03450 | Non-homologous end-joining | 2 (1.18%) | 7 (0.21%) | 4.59E-02 |

Supplementary Table S16. Kyoto encyclopedia of genes and genomes enrichment between EA group and Control group ($P < 0.05$).

| Pathway ID | Pathway | Diff Proteins with pathway annotation (115) | All Proteins with pathway annotation (3333) | <i>P</i> value |
|------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|----------------|
| ko00010 | Glycolysis / Gluconeogenesis | 11 (9.57%) | 42 (1.26%) | 8.88E-08 |
| ko03030 | DNA replication | 5 (4.35%) | 25 (0.75%) | 1.37E-03 |
| ko04612 | Antigen processing and presentation | 5 (4.35%) | 27 (0.81%) | 1.97E-03 |
| ko00051 | Fructose and mannose metabolism | 4 (3.48%) | 21 (0.63%) | 5.11E-03 |
| ko04141 | Protein processing in endoplasmic reticulum | 10 (8.7%) | 117 (3.51%) | 6.42E-03 |
| ko00030 | Pentose phosphate pathway | 4 (3.48%) | 25 (0.75%) | 9.71E-03 |
| ko04940 | Type I diabetes mellitus | 2 (1.74%) | 5 (0.15%) | 1.10E-02 |
| ko00750 | Vitamin B6 metabolism | 2 (1.74%) | 5 (0.15%) | 1.10E-02 |
| ko00020 | Citrate cycle (TCA cycle) | 4 (3.48%) | 28 (0.84%) | 1.45E-02 |
| ko05150 | Staphylococcus aureus infection | 2 (1.74%) | 6 (0.18%) | 1.62E-02 |
| ko05020 | Prion diseases | 3 (2.61%) | 20 (0.6%) | 2.97E-02 |
| ko05322 | Systemic lupus erythematosus | 3 (2.61%) | 21 (0.63%) | 3.38E-02 |

Supplementary Table S17. Kyoto encyclopedia of genes and genomes enrichment between BSN group and Control group ($P < 0.05$).

| Pathway ID | Pathway | Diff Proteins with pathway (29) | All Proteins with pathway annotation (3333) | P value |
|------------|-------------------------------------|---------------------------------|---------------------------------------------|-----------|
| ko05134 | Legionellosis | 3 (10.34%) | 34 (1.02%) | 2.96E-03 |
| ko03430 | Mismatch repair | 2 (6.9%) | 18 (0.54%) | 1.03E-02 |
| ko05020 | Prion diseases | 2 (6.9%) | 20 (0.6%) | 1.26E-02 |
| ko03030 | DNA replication | 2 (6.9%) | 25 (0.75%) | 1.94E-02 |
| ko03420 | Nucleotide excision repair | 2 (6.9%) | 26 (0.78%) | 2.09E-02 |
| ko04612 | Antigen processing and presentation | 2 (6.9%) | 27 (0.81%) | 2.24E-02 |
| ko04940 | Type I diabetes mellitus | 1 (3.45%) | 5 (0.15%) | 4.28E-02 |

Supplementary Table S18. Blood index of mice in Control group, BSN group, EA group and E@TSN group.

| Blood index | Unit | Control group | BSN group | EA group | E@TSN group | Reference value |
|-------------------------------------|---------------------|---------------|-----------|----------|-------------|-----------------|
| Erythrocytes | 10 ¹² /L | 8.54 | 8.64 | 8.52 | 10.30 | 10.30 |
| Leukocytes | 10 ⁹ /L | 4.86 | 4.51 | 4.08 | 4.64 | 4.87 |
| Platelet | 10 ⁹ /L | 468.00 | 786.00 | 800.00 | 800.00 | 693.40 |
| Hemoglobin | g/L | 129.00 | 123.00 | 149.00 | 158.00 | 160.70 |
| Hematocrit | % | 36.90 | 35.20 | 45.90 | 43.30 | 49.00 |
| Corpuscular volume | fL | 43.20 | 42.40 | 48.80 | 42.00 | 44.55 |
| Corpuscularhemoglobin | pg | 15.10 | 13.60 | 13.20 | 15.30 | 15.61 |
| Corpuscularhemoglobin concentration | g/L | 350.00 | 345.00 | 371.00 | 365.00 | 328.20 |
| Red Cell volume distribution width | % | 24.90 | 23.70 | 24.10 | 25.40 | 34.58 |

Supplementary Table S19. Biochemical indicator of mice in Control group, BSN group, EA group and E@TSN group.

| Biochemical indicator | Unit | Control group | BSN group | EA group | E@TSN group | Reference value |
|-----------------------|------|---------------|-----------|----------|-------------|-----------------|
| Total protein | g/L | 78.80 | 51.75 | 56.00 | 60.10 | 47.30 |
| Triglycerides | mM | 0.88 | 0.43 | 0.68 | 0.73 | 0.73 |
| Blood urea nitrogen | mM | 9.82 | 11.37 | 7.50 | 9.00 | 7.79 |
| Albumin | g/L | 31.10 | 24.85 | 25.50 | 26.40 | 32.90 |
| Glucose | mM | 3.67 | 3.28 | 5.19 | 4.28 | 3.58 |

Supplementary Methods

Solubility and oil-water partition coefficient assay. Apparent solubility was determined by adding excess EA and E@TSN to 5 mL of water or n-octanol in sealed glass containers at 25 °C. Each experiment was performed in triplicate. The liquids were agitated for 24 h, and then centrifuged to remove excess EA at 4,000 rpm for 10 min (TGL-16B Centrifuge, Anting Scientific Instrument, Shanghai, China). The supernatant was filtrated through a 0.45 µm membrane. The EA Concentration was analyzed by measuring the absorbance at 225 nm with an ultraviolet spectrometer. The standard regression equations for EA quantification was listed as follows: $A = 0.1775 C + 0.0411$, $r = 0.9995$ ($n = 3$), where A referred to the absorption of EA, C referred to the EA concentration, r referred to the correlation coefficient. The linearity range was 1.00-4.00 µg/mL. Apparent oil/water partition coefficient ($\log P$) studies were carried out using a shake flask method. Samples containing 5 mg EA were added to 10 mL of distilled water in sealed glass containers. The solutions were placed on a THZ-82A shaker (Ronghua Instrument Manufacturing Co., China) with a stirring at 100 rpm for 24 h at 37 °C. Following stirring, 10 mL of n-octanol was added to each solution and the mixture was agitated for another 24 h. The n-octanol and water phases were separated by centrifuging at 4000 rpm for 15 min, and filtrated through a 0.45 µm membrane. Finally, the EA concentrations were determined using a HPLC method. Each experiment was performed in triplicate. $\log P$ values of EA and E@TSN were calculated as follows: $\log P = C_o/C_w$, where C_o was the EA concentration in n-octanol, C_w was the EA concentration in water.

Optimal Preparation. E@TSN was successfully prepared through a solvent evaporation method. The optimal formula was obtained by a three-factor and five-level central composite design method (**Table S1**). The complex rate (CR) (between 27.82% and 85.80 %) of 20 batches changed significantly (**Table S2**). The fitting models are listed as follows:

$$y = 97.612 - 17.411X_1 + 2.589X_2 + 1.538X_3$$
$$(R^2 = 0.809, F = 27.869, P < 0.001) \quad (1)$$

$$y = 136.883 - 29.087X_1 - 10.239X_2 - 17.1$$
$$+ 1.829X_1X_3 + 5.687X_2X_3 \quad (2)$$

$$(R^2 = 0.764, F = 7.831, P = 0.002)$$

X_1 , X_2 and X_3 refer to EA (mol), PL/EA (mol/mol) and HCD/PL (mol/mol) respectively. As shown, linear model (Equation 1) of the experimental data is apparently superior to the quadratic model fitting (Equation 2) with respect to the correlation coefficient (R^2). According to Equation 1, when the reaction solvent (10 mL anhydrous ethanol), reaction time ($t = 5$ h) and the reaction temperature ($T = 60^\circ\text{C}$) were fixed, our results suggested that to develop a cost-effective E@TSN with high complexation rate, optimal values for X_1 (mol), X_2 (mol/mol) and X_3 (mol/mol) should be 1.85, 2.47, and 2.07, respectively. The CR of E@TSN prepared under the optimal protocol described was recorded as 85.80 ± 0.63 %. The predicted values and the experimental results of E@TSN prepared under the optimal protocol were consistent ($P > 0.05$) (**Table S2**).