

Table S1: Twenty most strongly upregulated genes in interleukin 4 -treated OA chondrocytes (IL4) relative to control (Co).

| Gene | Name | Function | Mean (Co) | Mean (IL4) | Fold Change | adj. p |
|---------|--|--|-----------|------------|-------------|-------------------------|
| KCNK3 | Potassium two pore domain channel subfamily K member 3 | Potassium ion transport | 4.2 | 41.0 | 12.97 | <1.0 × 10 ⁻⁴ |
| FGL2 | Fibrinogen like 2 | Negative regulation of antigen presentation? | 26.8 | 361.2 | 10.00 | <1.0 × 10 ⁻⁴ |
| SOCS1 | Suppressor of cytokine signaling 1 | Regulation of inflammation | 4.4 | 37.0 | 8.99 | <1.0 × 10 ⁻⁴ |
| MAOA | Monoamine oxidase A | Dopamine catabolism | 17.8 | 157.1 | 8.56 | <1.0 × 10 ⁻⁴ |
| CSN1S1 | Casein alpha s1 | Steroid signaling? | 6.8 | 20.8 | 6.16 | 2.5 × 10 ⁻⁴ |
| LRRC32 | Leucine rich repeat containing 32 | TGFβ signaling | 6.2 | 36.5 | 5.43 | 5.30 × 10 ⁻⁵ |
| FAM19A1 | Family with sequence similarity 19 member A1, C-C motif chemokine like | Neuroblast differentiation? | 4.0 | 17.5 | 5.04 | 0.0059 |
| OTOGL | Otogelin like | ? | 3.8 | 17.5 | 4.86 | 3.2 × 10 ⁻⁴ |
| SUCNR1 | Succinate receptor 1 | Metabolism and inflammation | 3.6 | 15.1 | 4.65 | 0.0018 |
| ANPEP | Alanyl aminopeptidase, membrane | Cell adhesion and inflammation | 88.3 | 408.8 | 4.41 | <1.0 × 10 ⁻⁴ |
| CADPS | Calcium dependent secretion activator | Exocytosis | 4.1 | 11.3 | 4.16 | 0.047 |
| SH2D1B | SH2 domain containing 1B | Regulation of inflammation | 7.3 | 27.7 | 4.12 | 2.90 × 10 ⁻⁵ |
| CISH | Cytokine inducible SH2 containing protein | Regulation of cell growth and inflammation | 16.0 | 64.6 | 4.08 | 2.3 × 10 ⁻⁴ |
| SELP | Selectin P | Cell adhesion and inflammation | 202.7 | 849.8 | 4.00 | <1.0 × 10 ⁻⁴ |
| SAMD3 | Sterile alpha motif domain containing 3 | ? | 4.3 | 17.3 | 3.95 | 0.0066 |
| CAPN8 | Calpain 8 | ? | 3.0 | 10.9 | 3.85 | 0.011 |
| LPL | Lipoprotein lipase | Lipid metabolism and inflammation | 15.1 | 44.1 | 3.65 | 1.0 × 10 ⁻⁵ |
| CYTIP | Cytohesin 1 interacting protein | Cell adhesion | 8.9 | 33.8 | 3.61 | 4.80 × 10 ⁻⁵ |
| RASL11B | RAS like family 11 member B | TGFβ signaling | 4.6 | 17.9 | 3.44 | 0.018 |
| MT-TW | Mitochondrially encoded trna tryptophan | ? | 24.7 | 60.6 | 3.38 | 2.3 × 10 ⁻⁴ |

Table S2: Genes downregulated with FC < -1.5 in interleukin 4 -treated OA chondrocytes (IL4) relative to control (Co)

| Gene | Name | Function | Mean (Co) | Mean (IL4) | Fold Change | adj. p |
|-----------------|--|--|-----------|------------|-------------|------------------------|
| <i>OSR1</i> | Odd-skipped related transcription factor 1 | Regulation of cell proliferation | 50.2 | 28.6 | -1.95 | 0.016 |
| <i>ANGPTL7</i> | Angiopoietin like 7 | Regulation of angiogenesis | 572.7 | 403.0 | -1.72 | 0.019 |
| <i>SCG5</i> | Secretogranin V | Regulation of protein aggregation | 164.7 | 109.6 | -1.59 | 0.035 |
| <i>OLFML2B</i> | Olfactomedin like 2B | ? | 84.9 | 50.7 | -1.56 | 0.025 |
| <i>NEK2</i> | NIMA related kinase 2 | Regulation of cell proliferation | 420.4 | 295.1 | -1.55 | 2.1 × 10 ⁻⁴ |
| <i>HIST1H4L</i> | Histone cluster 1 H4 family member l | ? | 178.3 | 136.3 | -1.54 | 0.026 |
| <i>NDC80</i> | NDC80, kinetochore complex component | Cell division | 821.8 | 578.4 | -1.53 | 5.0 × 10 ⁻⁶ |
| <i>RORC</i> | RAR related orphan receptor C | Regulation of cell differentiation and inflammation? | 148.9 | 105.2 | -1.52 | 0.027 |
| <i>AURKB</i> | Aurora kinase B | Regulation of cell proliferation | 164.0 | 114.5 | -1.52 | 0.0044 |
| <i>HMMR-AS1</i> | HMMR antisense RNA 1 | Regulation of cell motility? | 248.4 | 173.2 | -1.50 | 5.4 × 10 ⁻⁴ |

Table S3: GO terms enriched among the genes significantly affected by IL-4. The list of genes with FC > 1.5 in either direction and with FDR-corrected p-value < 0.05 was analyzed with DAVID, and the resulting list of GO terms was reduced with REVIGO.

| Term | adj. p |
|--|------------------------|
| Cell division | 2.45×10^{-11} |
| Chromosome segregation | 9.74×10^{-8} |
| Microtubule-based movement | 6.36×10^{-6} |
| CENP-A containing nucleosome assembly | 0.00035 |
| Protein localization to kinetochore | 0.00099 |
| Regulation of gene silencing | 0.0014 |
| Metaphase plate congression | 0.0018 |
| Protein heterotetramerization | 0.0027 |
| G2/M transition of mitotic cell cycle | 0.0029 |
| Telomere organization | 0.0030 |
| DNA replication-dependent nucleosome assembly | 0.0064 |
| Positive regulation of cytokinesis | 0.012 |
| Positive regulation of gene expression, epigenetic | 0.017 |
| Blood coagulation | 0.023 |
| DNA replication | 0.026 |
| Anaphase-promoting complex-dependent catabolic process | 0.049 |
| Cell proliferation | 0.049 |

Table S4: Genes markedly (FC > 2.5) upregulated in degraded OA cartilage compared to preserved in Almeida et al. [35] and significantly affected by proinflammatory cytokines in our study.

| Gene | Name | FC (Almeida) | FDR (Almeida) | FC (IL1 β) | adj. p (IL1 β) | FC (IL17) | adj. p (IL17) | FC (IFN γ) | adj. p (IFN γ) |
|------------------|---|-----------------|------------------------|----------------------|--------------------------|--------------|------------------|-----------------------|---------------------------|
| <i>IL11</i> | Interleukin 11 | 22.8 | 1.53×10^{-20} | 7.63 | <0.0001 | 3.31 | 0.00043 | - | - |
| <i>IGFBP1</i> | Insulin like growth factor binding protein 1 | 7.59 | 1.32×10^{-9} | 3.65 | <0.0001 | 3.06 | <0.0001 | 1.47 | <0.0001 |
| <i>TNP1</i> | Transition protein 1 | 6.6 | 2.60×10^{-5} | 15.70 | <0.0001 | 5.23 | 0.00019 | - | - |
| <i>ISM2</i> | Isthmin 2 | 5.24 | 4.71×10^{-18} | - | - | - | - | 3.90 | <0.0001 |
| <i>RIPK4</i> | Receptor interacting serine/threonine kinase 4 | 5.22 | 5.45×10^{-13} | 5.13 | <0.0001 | 2.12 | 0.00076 | - | - |
| <i>KPNA7</i> | Karyopherin subunit alpha 7 | 5.1 | 7.56×10^{-6} | 4.99 | <0.0001 | - | - | 2.42 | 0.0052 |
| <i>LIF</i> | LIF, interleukin 6 family cytokine | 4.91 | 7.79×10^{-10} | 30.92 | <0.0001 | 12.51 | <0.0001 | 1.59 | <0.0001 |
| <i>NGF</i> | Nerve growth factor | 4.91 | 2.53×10^{-14} | 4.86 | <0.0001 | - | - | 1.37 | 0.00027 |
| <i>TFPI2</i> | Tissue factor pathway inhibitor 2 | 4.08 | 9.92×10^{-9} | 26.93 | <0.0001 | 2.41 | <0.0001 | 1.27 | 0.0086 |
| <i>LAMC2</i> | Laminin subunit gamma 2 | 3.75 | 2.05×10^{-6} | 9.63 | <0.0001 | - | - | - | - |
| <i>CLIC3</i> | Chloride intracellular channel 3 | 3.65 | 1.81×10^{-11} | -3.23 | 0.00029 | - | - | 2.15 | <0.0001 |
| <i>TNFAIP6</i> | TNF alpha induced protein 6 | 3.58 | 2.48×10^{-8} | 36.87 | <0.0001 | 4.59 | <0.0001 | 3.59 | <0.0001 |
| <i>ERFE</i> | Erythroferrone | 3.44 | 8.82×10^{-12} | -3.36 | <0.0001 | 1.41 | 0.004 | -1.62 | <0.0001 |
| <i>PAPPA</i> | Pappalysin 1 | 3.43 | 1.14×10^{-10} | 6.46 | <0.0001 | 1.39 | 0.00015 | 1.57 | <0.0001 |
| <i>DNER</i> | Delta/notch like EGF repeat containing | 3.37 | 4.24×10^{-11} | 4.49 | <0.0001 | 2.66 | <0.0001 | - | - |
| <i>CCL20</i> | C-C motif chemokine ligand 20 | 3.35 | 5.10×10^{-5} | 1128.35 | <0.0001 | 73.49 | <0.0001 | - | - |
| <i>HMGA2</i> | High mobility group AT-hook 2 | 3.22 | 3.85×10^{-7} | 8.04 | <0.0001 | 5.34 | <0.0001 | 1.51 | 0.0018 |
| <i>BMPR1B</i> | Bone morphogenetic protein receptor type 1B | 3.2 | 1.28×10^{-7} | 6.94 | <0.0001 | 2.09 | 0.0049 | - | - |
| <i>LAMB3</i> | Laminin subunit beta 3 | 3.11 | 7.66×10^{-13} | 20.72 | <0.0001 | 3.42 | <0.0001 | - | - |
| <i>PTGES</i> | Prostaglandin E synthase | 3.06 | 3.61×10^{-12} | 5.72 | <0.0001 | 4.27 | <0.0001 | 2.04 | <0.0001 |
| <i>KRT16</i> | Keratin 16 | 3.03 | 1.22×10^{-5} | 36.58 | <0.0001 | - | - | - | - |
| <i>TNFRSF11B</i> | TNF receptor superfamily member 11b | 3.01 | 7.12×10^{-12} | 2.74 | <0.0001 | 3.12 | <0.0001 | -1.25 | 0.00021 |
| <i>SOX11</i> | SRY-box 11 | 2.99 | 1.62×10^{-8} | 3.64 | <0.0001 | - | - | -1.52 | 0.017 |
| <i>DNAJC12</i> | Dnaj heat shock protein family (Hsp40) member C12 | 2.97 | 5.10×10^{-5} | - | - | 3.33 | 0.044 | - | - |
| <i>KRT17</i> | Keratin 17 | 2.96 | 4.08×10^{-5} | 18.39 | <0.0001 | - | - | 5.21 | <0.0001 |
| <i>TRIM36</i> | Tripartite motif containing 36 | 2.85 | 1.08×10^{-8} | 7.06 | <0.0001 | - | - | - | - |
| <i>USP43</i> | Ubiquitin specific peptidase 43 | 2.77 | 0.00014 | 3.94 | 0.02 | 3.41 | 0.013 | 4.50 | 0.0091 |
| <i>GPR158</i> | G protein-coupled receptor 158 | 2.73 | 0.0036 | 9.98 | 2.50×10^{-5} | 6.77 | 0.0018 | 5.55 | 0.00076 |
| <i>SHISA9</i> | Shisa family member 9 | 2.73 | 4.47×10^{-5} | - | - | - | - | -2.72 | 2.90×10^{-5} |
| <i>NTF3</i> | Neurotrophin 3 | 2.72 | 6.59×10^{-6} | 2.98 | 0.00053 | - | - | - | - |
| <i>FAM167A</i> | Family with sequence similarity 167 member A | 2.67 | 1.91×10^{-7} | 3.54 | <0.0001 | 2.09 | 0.035 | - | - |
| <i>TREM1</i> | Triggering receptor expressed on myeloid cells 1 | 2.66 | 7.77×10^{-5} | 12.14 | <0.0001 | 2.47 | <0.0001 | -1.68 | 6.70×10^{-5} |
| <i>IGFBP3</i> | Insulin like growth factor binding protein 3 | 2.65 | 1.12×10^{-7} | 2.87 | <0.0001 | 1.89 | <0.0001 | -1.16 | 0.001 |
| <i>SLC27A2</i> | Solute carrier family 27 member 2 | 2.64 | 7.84×10^{-5} | -2.59 | 0.024 | - | - | -2.52 | 0.0073 |
| <i>ANK3</i> | Ankyrin 3 | 2.62 | 6.02×10^{-10} | -6.74 | <0.0001 | -3.02 | <0.0001 | -1.91 | <0.0001 |

| | | | | | | | | | |
|------------------------|---|-------------|-----------------------|--------------|-----------------------|-------------|---------|--------------|--------------|
| <i>DAW1</i> | Dynein assembly factor with WD repeats 1 | 2.57 | 2.55×10^{-5} | 2.96 | 8.00×10^{-6} | 2.44 | <0.0001 | -1.76 | 0.022 |
| <i>ANXA8</i> | Annexin A8 | 2.56 | 4.84×10^{-6} | 31.85 | 4.20×10^{-5} | - | - | - | - |
| <i>KLHL30- AS1</i> | Kelch like family member 30 | 2.5 | 0.0037 | - | - | 4.31 | 0.0067 | - | - |

Red = upregulated genes

Blue = downregulated genes

Table S5: Genes markedly (FC < -2.5) downregulated in degraded OA cartilage compared to preserved in Almeida et al. [35] and significantly affected by proinflammatory cytokines in our study.

| Gene | Name | FC (Almeida) | FDR (Almeida) | FC (IL1 β) | adj. p (IL1 β) | FC (IL17) | adj. p (IL17) | FC (IFN γ) | adj. p (IFN γ) |
|------------------|---------------------------------------|-----------------|------------------------|----------------------|--------------------------|--------------|------------------|-----------------------|---------------------------|
| <i>RCAN2</i> | Regulator of calcineurin 2 | -4.08 | 9.19×10^{-12} | -16.58 | <0.0001 | -4.74 | <0.0001 | -1.46 | 0.00015 |
| <i>VIT</i> | Vitrin | -3.91 | 1.14×10^{-8} | -2.96 | <0.0001 | -1.44 | 0.0008 | -1.95 | <0.0001 |
| <i>C3</i> | Complement C3 | -3.83 | 4.00×10^{-7} | 67.78 | <0.0001 | 33.70 | <0.0001 | - | - |
| <i>SHISA3</i> | Shisa family member 3 | -3.67 | 3.14×10^{-8} | -10.46 | <0.0001 | -2.11 | <0.0001 | -1.35 | 5.1×10^{-5} |
| <i>RSPO3</i> | R-spondin 3 | -3.62 | 1.48×10^{-6} | 47.37 | <0.0001 | 4.42 | <0.0001 | 2.08 | <0.0001 |
| <i>PTGER3</i> | Prostaglandin E receptor 3 | -3.08 | 4.91×10^{-8} | -2.69 | <0.0001 | -3.03 | <0.0001 | -2.82 | <0.0001 |
| <i>MATN4</i> | Matrilin 4 | -3.04 | 0.0028 | -2.59 | 0.022 | - | - | - | - |
| <i>GDF10</i> | Growth differentiation factor 10 | -2.86 | 1.05×10^{-8} | -20.57 | <0.0001 | -2.93 | <0.0001 | -1.70 | <0.0001 |
| <i>GDF7</i> | Growth differentiation factor 7 | -2.81 | 1.91×10^{-6} | -2.60 | 0.0001 | - | - | - | - |
| <i>NCMAP</i> | Non-compact myelin associated protein | -2.80 | 0.0012 | - | - | 4.08 | <0.0001 | - | - |
| | Cysteine rich secretory protein | | | | | | | | |
| <i>CRISPLD1</i> | LCCL domain containing 1 | -2.76 | 9.29×10^{-6} | -5.00 | <0.0001 | -3.39 | <0.0001 | - | - |
| <i>KIF1A</i> | Kinesin family member 1A | -2.70 | 8.64×10^{-8} | 4.59 | 0.00042 | - | - | - | - |
| | Dishevelled binding antagonist | | | | | | | | |
| <i>DACT1</i> | of beta catenin 1 | -2.68 | 2.85×10^{-7} | -4.13 | <0.0001 | - | - | 1.26 | 0.0079 |
| | Gremlin 1, DAN family BMP | | | | | | | | |
| <i>GREM1</i> | antagonist | -2.65 | 2.57×10^{-5} | -8.76 | <0.0001 | -3.41 | <0.0001 | - | - |
| <i>ZFHX4-AS1</i> | ZFHX4 antisense RNA 1 | -2.65 | 0.021 | -6.04 | 0.0001 | -2.77 | 0.012 | - | - |
| | KIT proto-oncogene receptor | | | | | | | | |
| <i>KIT</i> | tyrosine kinase | -2.58 | 0.00052 | 3.50 | 0.0072 | - | - | - | - |
| <i>ERICH3</i> | Glutamate rich 3 | -2.56 | 0.023 | -5.62 | <0.0001 | - | - | -2.64 | 0.0012 |
| <i>PRLR</i> | Prolactin receptor | -2.55 | 0.019 | 9.93 | <0.0001 | 3.05 | 0.0034 | 3.92 | 8.3×10^{-5} |
| <i>STEAP4</i> | STEAP4 metalloductase | -2.53 | 4.95×10^{-9} | -3.52 | <0.0001 | - | - | -1.79 | <0.0001 |

Red = upregulated genes

Blue = downregulated genes

Table S6: Genes markedly differentially expressed in degraded and preserved OA cartilage (with FC > 1.5 in either direction) in Almeida et al. [35] and markedly affected (with FC > 1.5 in either direction) by IL-4 in our study.

| Gene | Name | FC (Almeida) | adj. p (Almeida) | FC (our study) | adj. p (our study) |
|--|--|-----------------|------------------------|-------------------|-----------------------|
| <i>Genes upregulated in degraded cartilage (Almeida et al. [35]) and upregulated by IL-4 (our study)</i> | | | | | |
| <i>PTPRZ1</i> | Protein tyrosine phosphatase, receptor type Z1 | 1.94 | 0.019 | 2.62 | 0.0074 |
| <i>TMEM200A</i> | Transmembrane protein 200A | 1.87 | 0.0014 | 2.58 | <0.0001 |
| <i>POSTN</i> | Periostin | 2.06 | 0.032 | 2.32 | <0.0001 |
| <i>TENM3</i> | Teneurin transmembrane protein 3 | 1.90 | 4.08×10^{-5} | 2.08 | 1.40×10^{-5} |
| <i>TTC9</i> | Tetratricopeptide repeat domain 9 | 2.38 | 2.30×10^{-7} | 2.07 | 1.00×10^{-6} |
| <i>DUSP5</i> | Dual specificity phosphatase 5 | 1.51 | 0.031 | 1.97 | 0.0011 |
| <i>ANGPTL4</i> | Angiopoietin like 4 | 1.91 | 8.50×10^{-6} | 1.67 | 8.00×10^{-6} |
| <i>LRRC8C</i> | Leucine rich repeat containing 8 family member C | 2.36 | 5.88×10^{-8} | 1.65 | 0.00029 |
| <i>F5</i> | Coagulation factor V | 1.68 | 0.00084 | 1.50 | 0.04 |
| <i>COL7A1</i> | Collagen type VII alpha 1 chain | 2.37 | 1.96×10^{-8} | 1.50 | 0.0019 |
| <i>Genes upregulated in degraded cartilage (Almeida et al. [35]) and downregulated by IL-4 (our study)</i> | | | | | |
| <i>HMMR</i> | HMMR antisense RNA 1 | 1.78 | 0.047 | -1.50 | 0.00054 |
| <i>Genes downregulated in degraded cartilage (Almeida et al. [35]) and upregulated by IL-4 (our study)</i> | | | | | |
| <i>FGL2</i> | Fibrinogen like 2 | -1.71 | 0.0093 | 10.00 | <0.0001 |
| <i>CISH</i> | Cytokine inducible SH2 containing protein | -2.24 | 4.71×10^{-18} | 4.08 | 0.00023 |
| <i>GPM6A</i> | Glycoprotein M6A | -1.73 | 0.015 | 2.25 | 0.044 |
| <i>COL14A1</i> | Collagen type XIV alpha 1 chain | -1.75 | 0.033 | 2.11 | <0.0001 |
| <i>CYSLTR1</i> | Cysteinyl leukotriene receptor 1 | -1.68 | 0.00085 | 1.96 | 0.00072 |
| <i>DKK1</i> | Dickkopf WNT signaling pathway inhibitor 1 | -1.66 | 0.018 | 1.86 | 0.028 |
| <i>CORO2B</i> | Coronin 2B | -1.82 | 0.0001 | 1.60 | 0.014 |

Red = upregulated genes

Blue = downregulated genes

Table S7: Expression of central cytokine receptors in unstimulated chondrocytes. Mean expression values are given as DESeq2-normalized counts.

| Gene | Mean (Co) |
|--------|-----------|
| IL1R1 | 2448.7 |
| IL4R | 65.6 |
| IL17RB | 210.5 |
| IL17RC | 349.1 |
| IL17RD | 66.1 |
| IL17RE | 14.3 |
| IFNGR1 | 1529.5 |
| IFNGR2 | 1501.3 |