Periarticular mesenchymal progenitors initiate and contribute to secondary ossification center formation during mouse long bone development

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Running title: Periarticular MSCs form the SOC

Supplementary Figure

Figure S1

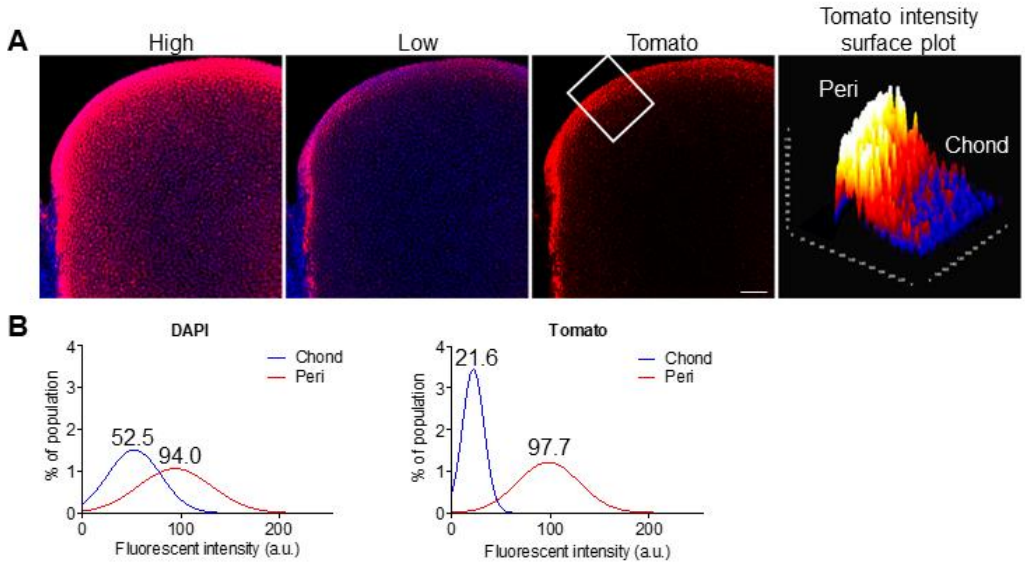

Figure S1 Periarticular cells show increased Tomato fluorescence compared to the underlying chondrocytes prior to SOC initiation.

(**A**) Epiphyseal femurs were imaged for tomato fluorescence and a surface plot of Tomato fluorescence along the outer surface generated. Bar = 50 µm. (**B**) Fluorescent intensity distribution of the periarticular region and underlying chondrocytes for DAPI and Tomato. Numbers indicate mean value of group.

Figure S2

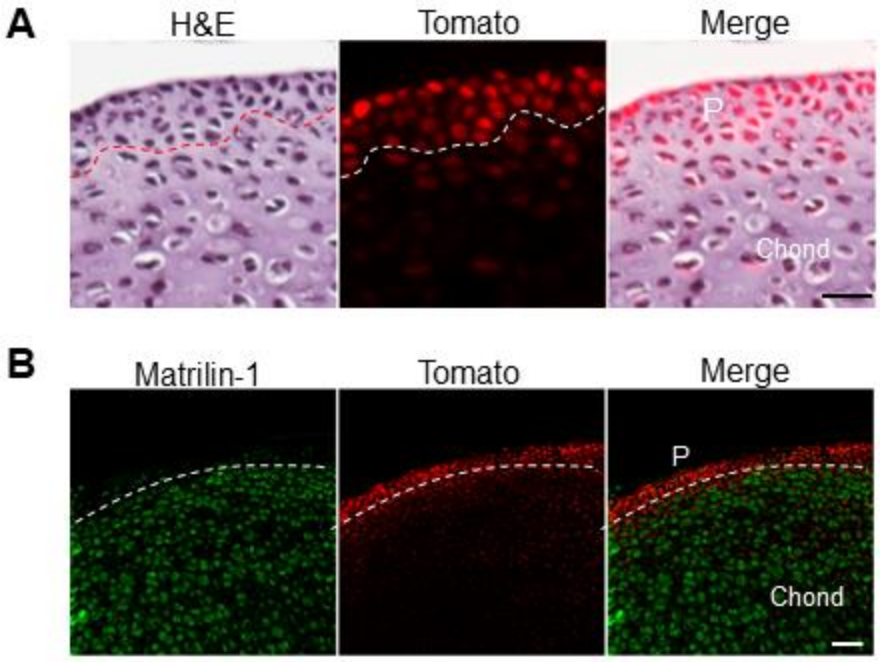

Figure S2 Tomato^{H} cells correspond with the periarticular region while Tomato^{L} cells of the underlying chondrocytes are destined for removal during SOC formation.

(**A**) Overlay between fluorescent and H&E stained images show that the Tomato^{H} cells correspond with the outer layer of periarticular cells while the Tomato^{L} cells represent the underlying chondrocytes. Dotted lines denote periarticular cell-epiphyseal chondrocyte boundary. Bar = 50 μm. (**B**) Tomato^{H} and Matrilin-1 cells segregate, suggesting Tomato^{H} cells remain to form the articular cartilage while the Tomato^{L} cells will be removed during epiphyseal marrow compartment formation. Dotted line denotes Tomato^{H}-Matrilin-1^{+} boundary. Bar = 100 μm.

Figure S3

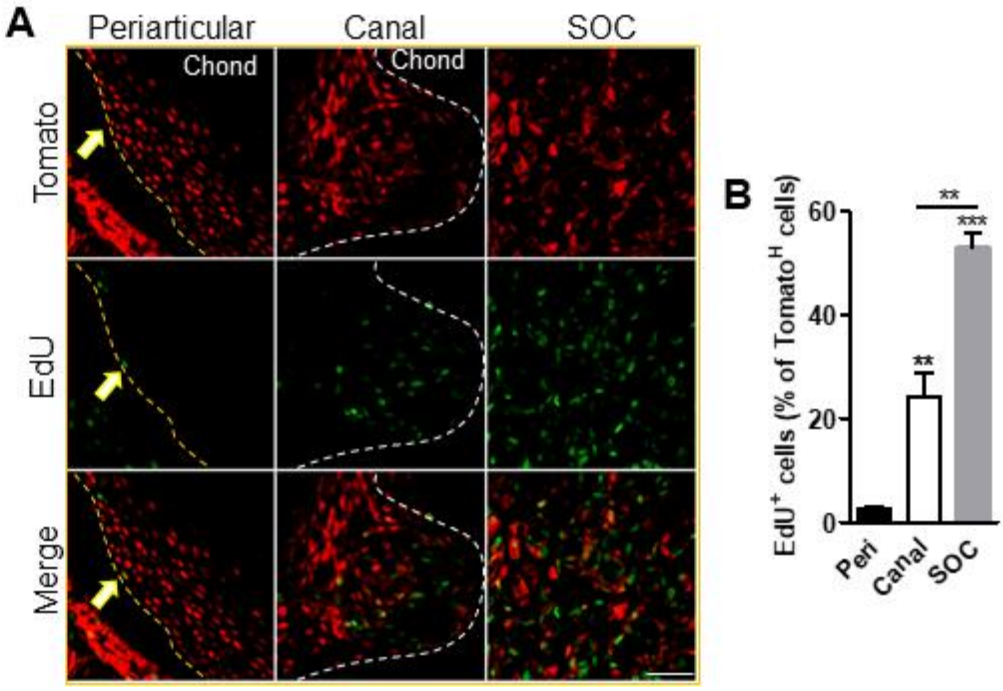

Figure S3 Periarticular invasion during SOC canal progression is associated with increased cellular proliferation.

(**A**) *Col2/Tomato* mice were injected with EdU then imaged by confocal microscopy in the periarticular region, invading canal or expanding SOC. Dotted lines denote the periarticular surface (yellow) and canal front (white), respectively. Yellow arrow points to periarticular surface. Bar = 50 µm. (**B**) The percent of $Tomato^{H}$ cells staining positive for EdU were quantified. Graphs represent average values ± SEM. Data analyzed by one-way ANOVA. (*$p<0.05$, **$p<0.01$) (n=6).

Figure S4

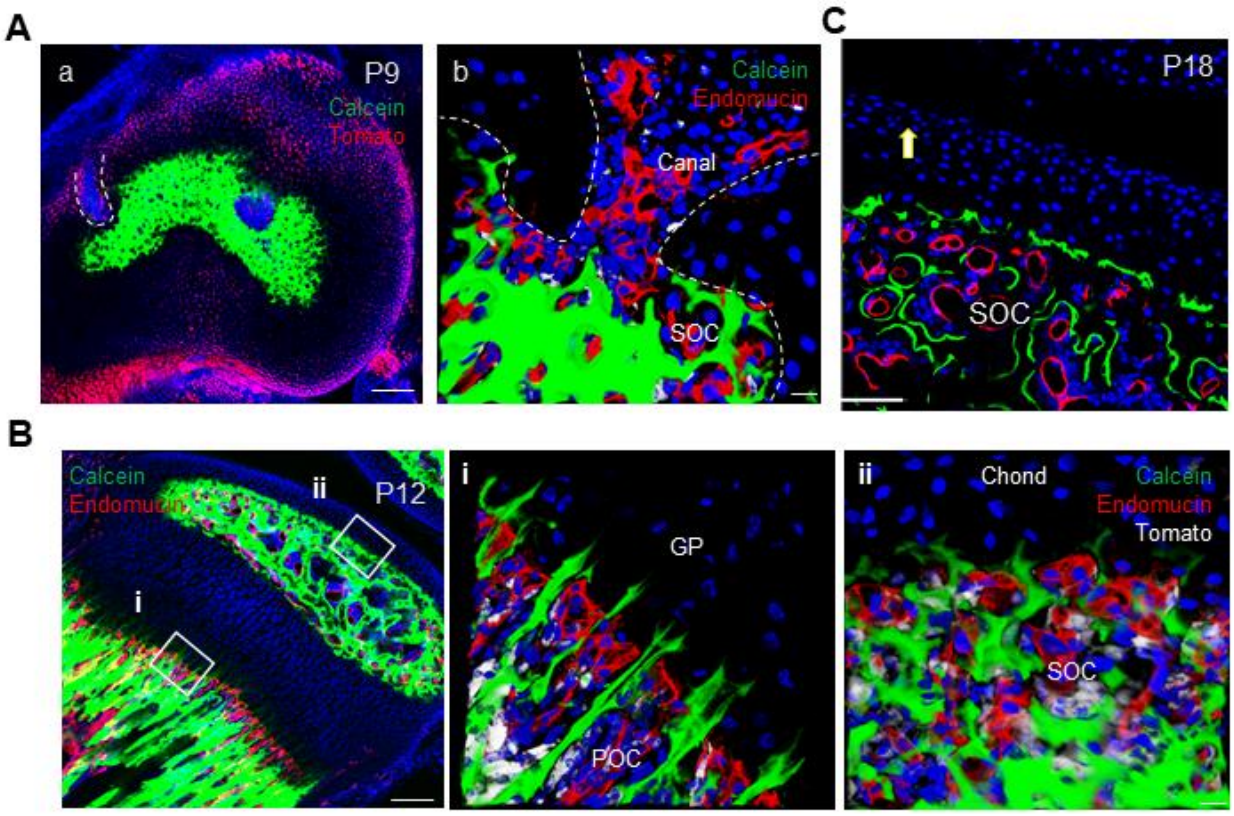

Figure S4 Mineralization directs vessel-led outward SOC expansion, but not Tomato^{H} driven canal invasion.

(**A**) Calcein labeling shows intense mineralization occurring in the forming SOC, but not along the invading canal. Dotted white line shows canal and SOC structure. Bar = 200 μm (a), 20 μm (b). (**B**) Calcein labeling shows mineralization between chondrocytes parallel to the direction of SOC expansion at and ahead of vessel invasion at P12, reminiscent of POC expansion. Bar = 200 μm, 20 μm. (**C**) However, at the later stages of SOC maturation, mineralization seems transition to perpendicular, slowing SOC expansion and establishing articular cartilage boundaries around P18. Bar = 50 μm.

Figure S5

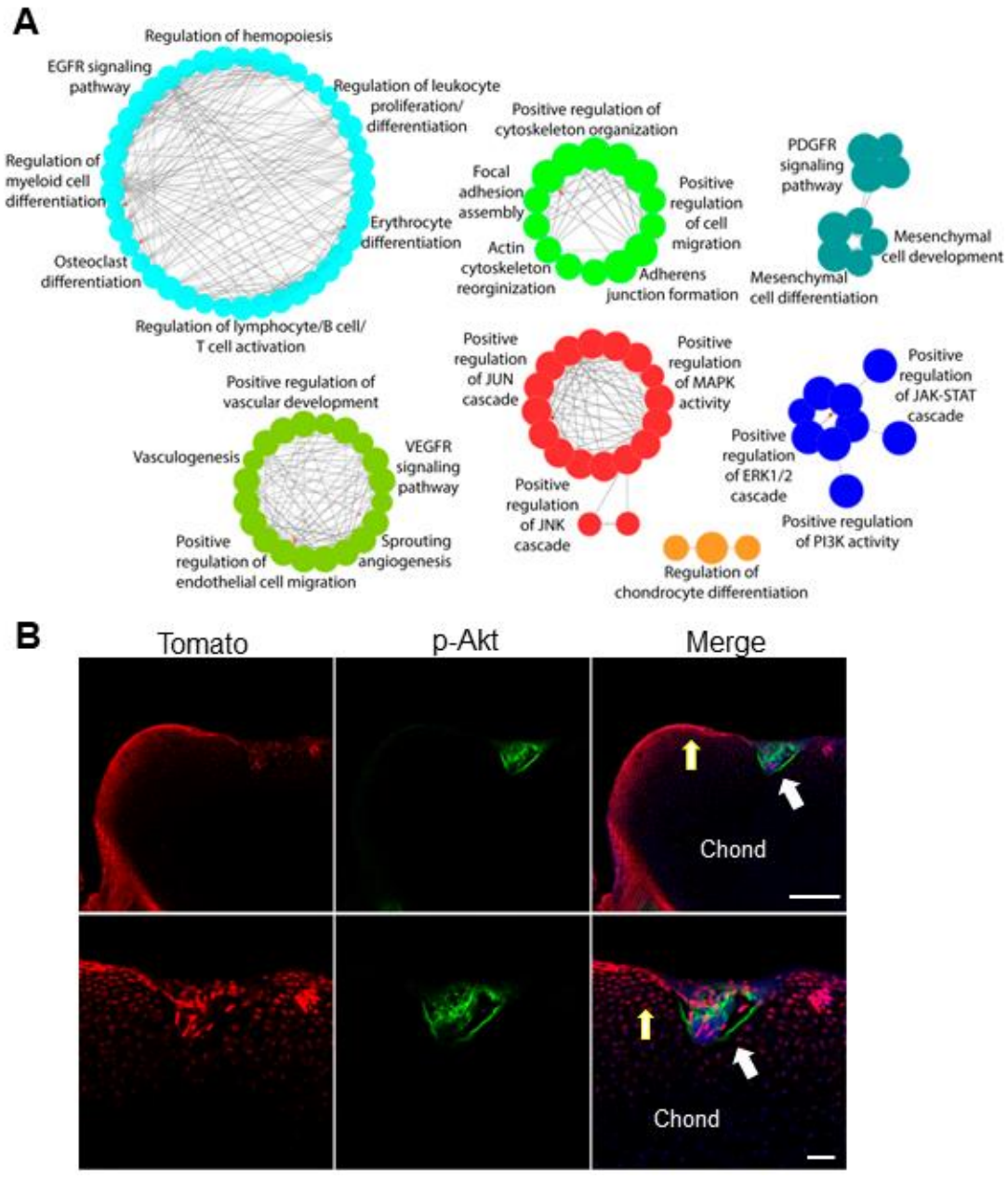

Figure S5 Gene expression analyses associated with canal initiation and progression.

(**A**) KEGG pathways found to be significantly regulated in the canal, relative to peri, were subjected to GO term cluster analyses. Along with large clusters related to myeloid cell migration, differentiation, and activation, as well as in blood vessel development, GO term clusters were observed for regulation of cell adhesion and related signaling, mesenchymal cell differentiation, and kinase signaling through the MAPK

and ERK1/2 cascades. (**B**) Immunofluorescent staining of activated p-Akt during early canal initiation. Yellow arrow denotes perichondrium and white arrow denotes SOC canal.

Table S1 Mouse real-time PCR primer sequences used for this study.

Gene	Forward primer	Reverse primer
β-actin	5'-TCCTCCTGAGCGCAAGTACTCT-3'	5'-CGGACTCATCGTACTCCTGCTT-3'
Col2	5'-GCTCCCAGAACATCACCTACCA-3'	5'-TCATTGGAGCCCTGGATG-3'
Col10	5'-GCCCGTGTCTGCTTTTACTGTC-3'	5'-GGTCGTAATGCTGCCTAT-3'
Sox9	5'-CCAACATTGAGACCTTCGACGT-3'	5'-ATGCCTAACTGCCAGTGTAGG-3'
Osterix	5'-AGAGGTTCACTCGCTCTGACGA-3'	5'-TTGCTCAAGTGGTCGCTTCTG-3'
IBSP	5'-ACCAGTTATGGCACCACGACA-3'	5'-TCAACCGTGCTGCTCTTTCTG-3'
Ocn	5'-GGCGCTACCTGTATCAATGG-3'	5'-TCAGCCAACTCGTCACAGTC-3'
Opn	5'-CTGGATGACCAGAGTGCTGA-3'	5'-TGAAATTCATGGCTGTGGAA-3'
Pparγ	5'-CCAGCGTGAAGCCAGAGTAG-3'	5'-ACCGTGGCTGTGCTCATCCT-3'
Cebpα	5'-GGCCAAGAAGTCGGTGGATAA-3'	5'-GGAGAAGGCATGCTCATGTT-3'
Lpl	5'-GCGCTCCATCCATCTCTTCAT-3'	5'-GGCAGAGCCCTTTCTCAAATG-3'

Table S2 ECM genes significantly regulated in the periarticular region (Peri) versus the underlying chondrocytes (Chond).

	Gene		Fold Change
Enriched in Peri	*Col1a1*	collagen, type I, alpha 1	9.08
	Col1a2	collagen, type I, alpha 2	6.20
	Col3a1	collagen, type III, alpha 1	2.91
	Col8a1	collagen, type VIII, alpha 1	3.03
	Col14a1	collagen, type VIX, alpha 1	4.21
	Col15a1	collagen, type VX, alpha 1	2.37
	Fn1	fibronectin 1	2.59
	Eln	elastin	6.66
Enriched in Chond	*Col2a1*	collagen, type 2, alpha 1	3.64
	Col9a1	collagen, type IX, alpha 1	5.68
	Col9a2	collagen, type IX, alpha 2	5.08
	Col9a3	collagen, type IX, alpha 3	3.56
	Col11a1	collagen, type XI, alpha 1	4.24
	Col11a2	collagen, type XI, alpha 2	2.33
	Acan	aggrecan	2.90
	Hapln1	hyaluronan and proteoglycan link protein	3.24

Table S3 Differentially expressed genes in the cartilage underneath the canal (CNC) versus neighboring epiphyseal chondrocytes (Chond).

Fold Change	P-val	FDR P-val	Gene Symbol
153.77	5.13E-09	0.0002	Mmp13
93.36	0.0026	0.6018	Spp1
17.17	0.0208	0.815	Dpt
9.24	4.46E-09	0.0002	Mmp9
7.59	0.0193	0.815	Gjc3
7.53	0.0397	0.8485	Efemp1
6.6	0.0164	0.8042	Gpr137b-ps
6.23	4.67E-06	0.0616	Loxl4
5.63	8.76E-05	0.2223	Gm13767
5.1	0.0019	0.5813	Lef1
4.88	0.0005	0.4232	Vdr
4.52	0.0011	0.4889	Gm18953
4.33	0.001	0.4831	Gm15899
4.25	0.0128	0.7964	Ttyh2
4.24	0.0016	0.5549	Shox2
4.11	0.0093	0.7444	Cd68
3.97	0.0036	0.6605	Bmp5
3.96	0.0085	0.7316	Serpina3n
3.94	0.0405	0.8489	Cdh5
3.79	0.0032	0.6247	Slc14a1
3.72	0.0006	0.4232	Usp53
3.62	0.0088	0.7349	Plekhg1
3.53	0.0099	0.7444	Gm13295
3.42	0.0241	0.825	Runx2
3.4	0.0102	0.7444	Gpr137b
3.37	0.0012	0.5061	Fn1
3.26	0.0398	0.8485	Kdm7a
3.22	0.0414	0.8489	Atp6v0d2
3.22	0.0101	0.7444	Ccdc80
3.19	0.0062	0.6715	Avpr1a
3.19	0.006	0.6715	Slc13a5
3.11	0.0092	0.7444	Adm
3.1	0.0113	0.7726	Plxnd1
3.07	0.0312	0.8284	Lgmn

3.04	0.0091	0.7418	Slc25a5
2.97	0.0096	0.7444	Gm16128
2.96	0.0003	0.3632	Gm14897
2.92	0.0005	0.4232	Spcs3
2.89	0.0009	0.4786	Ddx21
2.88	0.0041	0.667	Qpctl
2.83	0.018	0.8128	Unc5c
2.78	0.0079	0.7189	Gm2260
2.78	0.004	0.667	Extl1
2.76	0.0137	0.8005	Cirh1a
2.76	0.0001	0.2229	Tpcn1
2.73	0.0013	0.5276	Serinc5
2.71	0.0058	0.6715	Plxna2
2.68	0.0409	0.8489	Cldn34c2; Gm6604
2.68	0.0219	0.8164	Nacc1
2.68	0.0007	0.4591	Ptch1
2.67	0.0002	0.2769	Kcns1
2.62	0.013	0.7971	Actr1a
2.61	0.0029	0.6118	Tyrobp
2.55	0.0064	0.6715	Ctsc
2.53	0.0321	0.8309	Erg
2.52	0.0086	0.7322	Cpm
2.52	0.002	0.5813	Gm525
2.49	0.0218	0.8164	Ipo11
2.49	0.0195	0.815	Erbb2
2.49	0.0022	0.5813	Nploc4
2.49	0.0022	0.5813	Epha2
2.48	0.0424	0.849	Slc1a1
2.48	0.0027	0.6018	Ust
2.47	0.0217	0.8164	Pde11a
2.47	0.0159	0.8042	Hey1
2.45	0.0011	0.4889	Prr5
2.41	0.0003	0.3637	Mpi
2.4	0.0092	0.7444	Gm2274
2.36	0.0325	0.8324	Fzd4
2.34	0.007	0.6837	Uck2
2.33	0.016	0.8042	Cdkn1a
2.32	0.0076	0.7098	Gcnt2
2.32	0.0039	0.667	Runx1
2.3	0.0055	0.6675	Myo1d
2.3	0.0021	0.5813	Ptprf
2.3	0.0017	0.558	Kars
2.29	0.0086	0.7322	Hipk2

2.27	0.0412	0.8489	Ebf3
2.27	0.0064	0.6715	Alg3
2.27	0.0052	0.667	Muc1
2.26	0.0059	0.6715	Gatad2a
2.25	0.0074	0.7034	Lcp1
2.24	0.0263	0.8258	Cspg4
2.24	0.0014	0.5332	Srgap1
2.22	0.0053	0.667	Gm5762
2.22	0.0012	0.5054	Gm8822
2.21	0.019	0.815	Mgp
2.19	0.0014	0.5276	Chil1
2.18	0.0191	0.815	Snap29
2.15	0.0132	0.8	Cd302
2.15	0.0009	0.4786	Tnfrsf21
2.15	0.0005	0.4232	Gpc1
2.14	0.0045	0.667	Trim8
2.14	0.0008	0.4786	Sema7a
2.11	0.0117	0.7784	Fos
2.11	0.0101	0.7444	Btg1
2.1	0.0249	0.825	Lgals3
2.1	0.0134	0.8	Rgl1
2.09	0.0092	0.7444	Ppil4
2.09	0.0008	0.4747	Lrrc59
2.08	0.0342	0.8398	Skap2
2.08	0.0116	0.7784	Hsd17b7
2.05	0.0268	0.826	Tgm2
2.04	0.0291	0.8284	Bcl6
2.04	0.0078	0.7107	Ube3c
2.04	0.0033	0.6255	Osbpl11
2.03	0.0059	0.6715	Grb14
2.03	0.0042	0.667	Agps
2.03	0.0016	0.5549	Mgat4a
2.03	0.0004	0.3944	Ywhah
2.03	2.06E-05	0.1046	Hmgxb3
2.01	0.0004	0.3944	Wdr37
2.01	4.15E-05	0.1563	Pitpnc1
2	0.0357	0.8468	Cd86
2	0.0162	0.8042	Ppp1r3b; Gm20359
2	0.0154	0.8042	Kctd5
-2.01	0.0201	0.815	Clybl
-2.02	0.0398	0.8485	Cast

-2.03	0.0292	0.8284	Zfp101
-2.04	0.0455	0.8518	Lyrm4
-2.04	0.0441	0.8506	Cth
-2.05	0.0436	0.8506	Ankra2
-2.07	0.0413	0.8489	Apln
-2.07	0.0139	0.8005	Cdc20
-2.07	0.0077	0.7098	Atg14
-2.07	0.0009	0.4786	Lsm10
-2.08	0.0418	0.849	ND3
-2.08	0.0399	0.8485	Tmem179b
-2.09	0.0219	0.8164	Triqk
-2.12	0.0413	0.8489	Csrp2
-2.12	0.0113	0.7726	Trappc6a
-2.13	0.0015	0.5459	Zfp639
-2.15	0.016	0.8042	1700029J07Rik
-2.15	0.0064	0.6715	2610318N02Rik
-2.15	0.0062	0.6715	Arl4a
-2.16	0.0458	0.8518	Hmgb2
-2.16	0.0203	0.815	Tpbg
-2.17	0.001	0.483	Sclt1
-2.18	0.0002	0.2769	Fam189a1
-2.19	0.0307	0.8284	4930452B06Rik
-2.19	0.0259	0.8254	Ppm1k
-2.2	0.0009	0.4786	Cetn4
-2.21	0.047	0.8547	Siva1
-2.22	0.0213	0.815	Morn2
-2.23	0.0313	0.8284	Pter
-2.25	0.0281	0.8261	Fuca1
-2.27	0.0106	0.7559	Ap4s1
-2.27	0.0094	0.7444	Xlr
-2.28	0.0372	0.8474	Tspan2
-2.28	0.0203	0.815	Igfals
-2.28	0.0042	0.667	Ivd
-2.29	0.0166	0.8042	Hs6st2
-2.3	0.0007	0.4541	Gm11110
-2.33	0.0175	0.8124	Gm18284
-2.33	0.0094	0.7444	Uqcc3
-2.33	0.0075	0.7098	Cilp
-2.34	0.0317	0.8294	Mrpl42
-2.34	0.023	0.824	Ndufaf1
-2.34	0.0099	0.7444	Slc27a6
-2.34	0.0062	0.6715	Mir181a-1; Mir181b-1
-2.35	0.0007	0.4591	S100a6

-2.35	0.0006	0.4232	Tmem107
-2.36	0.0433	0.8502	Gm10509
-2.37	0.0002	0.314	Sgce
-2.38	0.0322	0.8321	Fam134c
-2.38	0.0243	0.825	Arl6ip1
-2.39	0.0175	0.8124	1810062G17Rik
-2.41	0.0028	0.6048	Kazald1
-2.41	0.0001	0.2229	Wls
-2.42	0.02	0.815	Gdf10
-2.42	0.0039	0.667	Ccpg1os
-2.43	0.0009	0.4786	Tmem98
-2.45	0.0327	0.8349	Id2
-2.46	0.0138	0.8005	Ndrg2
-2.49	1.15E-05	0.0949	Zfp273
-2.52	0.0321	0.8318	Dleu2; Mir16-1; Gm20034
-2.53	0.0242	0.825	Gm11114
-2.53	0.0182	0.8128	Emp2
-2.53	0.0113	0.7738	Ddah1
-2.54	0.0475	0.8547	Pgrmc1
-2.56	0.0376	0.8474	Robo1
-2.56	0.0298	0.8284	Plxdc2
-2.57	9.47E-05	0.2229	Zfp85
-2.6	0.0334	0.8371	Gm15452
-2.61	0.0027	0.6018	Map2k5
-2.63	0.0131	0.7988	Osr2
-2.64	0.0058	0.6715	D10Jhu81e
-2.64	0.0031	0.6118	Gm17728
-2.64	0.0001	0.2304	Arxes1
-2.65	0.0296	0.8284	Cdkn3
-2.65	0.014	0.8005	Rnf170-ps
-2.65	0.0018	0.5813	Lmo1
-2.68	0.0083	0.7278	Fam83d
-2.7	0.0182	0.8128	Sppl2a
-2.71	0.001	0.4841	Trip13
-2.71	0.0003	0.3425	Tmem203
-2.76	0.011	0.7679	Gm6169
-2.77	0.0286	0.8262	Gm19945
-2.79	0.0148	0.8042	Rabac1
-2.8	0.0172	0.8099	Fzd8
-2.81	0.0043	0.667	Adhfe1

-2.83	0.0233	0.825	Pdgfd
-2.84	3.27E-05	0.154	C130060K24Rik
-2.86	0.0108	0.7647	Agtr2
-2.86	0.0086	0.7322	Gm17530
-2.86	0.0044	0.667	Nthl1
-2.88	0.0155	0.8042	Zfp654
-2.9	0.0134	0.8	Pemt
-2.92	0.0002	0.3059	Six1
-2.96	1.49E-05	0.0949	Spry3
-2.98	0.0102	0.7444	Pemt
-3.06	0.0254	0.8254	Gstk1
-3.11	0.0379	0.8474	Fkbp7
-3.11	0.0053	0.667	Calml3
-3.16	0.0022	0.5813	Meis2
-3.33	0.018	0.8128	Depdc1a
-3.35	0.0255	0.8254	Gm8707
-3.37	0.0023	0.5831	Lrrc17
-3.4	0.0009	0.4786	Nrn1
-3.51	1.75E-05	0.0962	Nipal2
-3.55	0.0088	0.7349	Spry2
-3.55	0.0023	0.5865	Mab21l2
-4	8.61E-05	0.2223	Sap30
-4.03	0.003	0.6118	Pemt
-4.15	0.0058	0.6715	Sulf2
-4.56	0.0242	0.825	Sema3e
-4.65	0.0185	0.815	Pon3
-4.65	6.67E-05	0.1914	Gpc3
-4.74	0.0211	0.815	Egfl6
-4.81	0.0315	0.8292	Hhip
-4.85	1.58E-05	0.0949	Ecm2
-5.34	0.0079	0.7189	Ndufa4l2
-5.37	0.0167	0.8042	Grem1
-5.61	7.08E-06	0.0667	Angptl1
-5.76	0.011	0.7679	Dcx
-5.96	0.0456	0.8518	Abi3bp
-6.13	0.0022	0.5813	AF357426
-6.56	0.0153	0.8042	3830403N18Rik

-7.13	0.0202	0.815	Egln3
-7.28	0.0011	0.4889	Creb5; 9430076C15Rik
-11.57	0.0269	0.826	Gm11168
-13.7	0.0252	0.8254	Gm10717
-14.56	0.0119	0.7784	Hoxd10
-15.69	0.0342	0.8396	Gm17535
-16.4	0.008	0.719	Gm21738
-16.98	0.0229	0.8239	Gm10719
-17.75	0.0207	0.815	Gm10720
-17.94	0.0196	0.815	Gm10715
-19.05	0.0205	0.815	Gm10718; Gm10722
-20.34	0.0217	0.8164	Gm10721
-20.47	0.0064	0.6715	Mir300
-25.19	0.0359	0.8474	Gm10801
-39.87	0.0023	0.5865	Wif1
-61.82	0.0205	0.815	Gm10800
-1521.53	0.0002	0.2769	Prg4

Table S4 Differentially expressed genes in the cartilage canal (Canal) versus the periarticular region (Peri).

Fold Change	P-val	FDR P-val	Gene Symbol
237.07	2.12E-09	6.99E-05	Mmp13
231.7	7.95E-13	5.24E-08	Mmp9
58.6	0.0009	0.1184	Spp1
39.49	5.00E-07	0.0033	Bcl2a1a
25.17	1.56E-06	0.0058	Mmp10
21.42	6.52E-05	0.024	Mpeg1
15.29	0.0137	0.4973	Mcpt4
14.86	0.0114	0.4606	Clec7a
14.81	7.01E-05	0.025	Cd68
14.62	2.35E-05	0.014	Cd74; Mir5107
14.59	0.0143	0.5042	Cpa3
13.83	1.22E-07	0.0013	Ccl3

13.57	0.0006	0.0878	Map3k7cl
13.27	0.0004	0.0704	Lst1
12.67	0.0001	0.039	Aplnr
12.57	4.12E-05	0.0211	Atp6v0d2
11.54	0.0023	0.2016	Cdh5
11.28	5.10E-06	0.0099	Rac2
10.8	8.40E-05	0.0284	Plxnd1
10.27	9.85E-05	0.0306	Gpr137b
9.93	0.0003	0.053	Mcam
9.74	0.0145	0.5062	Igsf6
9.61	0.0053	0.3179	Sele
9.61	0.0002	0.0391	H2-Ab1
9.37	0.0002	0.0447	Gpr137b-ps
8.96	0.0002	0.0447	Serpina3n
8.79	0.0025	0.207	Pecam1
8.63	0.0068	0.3658	Slitrk6
8.44	3.44E-08	0.0008	Podnl1
7.91	8.86E-08	0.0012	Sema7a
7.78	0.0003	0.0559	Ms4a7
7.72	0.0145	0.5062	Cd93
7.28	2.03E-05	0.0128	Bcl2a1b; Bcl2a1a
6.97	0.004	0.272	Gm15079
6.67	0.0008	0.1098	Emcn
6.49	0.0471	0.7731	Hsd11b2
6.39	0.0001	0.0347	Adgrl4
6.35	0.0002	0.0391	Apln
6.16	5.58E-07	0.0033	Cotl1
6.08	0.007	0.3709	Vcl
6.08	0.0003	0.0571	Myo10
6.07	0.0004	0.0636	Fcer1g
6.06	0.0003	0.05	Acta2
6	1.22E-05	0.01	Tlr13
5.9	0.0162	0.5289	Pdgfrb
5.76	6.21E-05	0.0232	Cnn2

5.67	0.0009	0.1111	Cd84
5.65	0.0001	0.0329	Kcne3
5.62	7.77E-07	0.0043	Lcp1
5.59	0.001	0.126	Cxcl16
5.57	0.0021	0.1908	Avpr1a
5.49	0.0133	0.4902	Kitl
5.48	0.0023	0.1984	Rspo3
5.48	1.35E-07	0.0013	Clec4a2
5.45	0.0002	0.0391	Myo1e
5.39	0.0119	0.4683	Tpsb2
5.39	0.0149	0.5112	Fabp4
5.38	1.06E-05	0.01	H2-Eb1
5.37	0.0158	0.5247	Trgj1; Tcrg-C1
5.18	2.95E-05	0.0168	Clec4a1
5.12	0.0177	0.5489	Tcrg-C3
4.97	0.0002	0.0447	Ctsc
4.94	1.41E-05	0.01	Tyrobp
4.89	0.0005	0.0792	Apobec1
4.87	0.0002	0.0391	Tek
4.86	0.0042	0.2789	Ccl8
4.84	6.13E-06	0.01	Clec4n
4.83	7.48E-06	0.01	Akr1b8
4.62	7.99E-06	0.01	Cstb
4.6	0.0038	0.2652	Nrp1; Mir1903
4.51	7.81E-06	0.01	Nckap1l
4.46	0.007	0.3709	Flna
4.45	0.0002	0.0447	Apod
4.38	0.0012	0.1413	Il1r1
4.38	0.0001	0.0351	Rap2a
4.34	0.0003	0.0493	Csf2rb; Mir7676-1; Mir7676-2
4.34	0.0076	0.3833	Slc1a1
4.33	0.0101	0.4294	Ms4a14
4.32	0.0012	0.1388	Foxs1
4.32	0.0127	0.4813	Kdr
4.2	0.0038	0.2665	Lyz2

4.14	3.05E-05	0.017	Cs
4.09	2.26E-05	0.0138	Serpine2
4.04	0.0001	0.0356	Plk2
3.96	0.0132	0.4897	Mmrn2
3.95	0.0011	0.1295	Jag1
3.91	0.0163	0.5298	Mnda
3.9	7.66E-06	0.01	Bcl2a1d
3.89	2.29E-05	0.0139	Sstr2
3.89	0.0001	0.0346	Lpl
3.88	0.0008	0.1072	Timp1
3.87	0.0033	0.2443	Fzd4
3.84	0.0009	0.1163	Dusp6
3.81	1.35E-05	0.01	Ptk2b
3.78	0.0235	0.6125	Cxcl14
3.77	0.0002	0.0429	Laptm5
3.77	0.0003	0.048	Loxl4
3.72	8.80E-05	0.0287	Pgf
3.72	0.0038	0.2656	Hpgds
3.67	0.013	0.4861	Ccr1
3.66	1.25E-06	0.0055	Actg2
3.64	9.75E-05	0.0305	Adam19
3.62	0.0001	0.0385	Fabp5
3.59	0.0189	0.5618	Slc7a7
3.59	0.0383	0.7273	St5
3.59	0.0038	0.2665	Nrp2
3.56	0.0008	0.1045	Skap2
3.55	0.0025	0.207	Steap4
3.55	0.0014	0.1498	Slc25a5
3.51	0.0012	0.1394	Vcam1
3.48	0.0215	0.5913	Hey1
3.48	0.0002	0.0447	Atp6v1b2
3.46	0.0019	0.1771	Npl
3.44	0.0012	0.1373	sept11
3.43	0.0071	0.3719	Dhcr24
3.43	0.0042	0.2783	Sh3pxd2b
3.42	0.0222	0.5996	Ednrb

3.42	0.0006	0.0919	Svep1
3.38	0.0186	0.5601	Pdgfd
3.37	0.0051	0.3135	Slco2a1
3.36	0.0008	0.1038	Lgmn
3.33	0.0009	0.1184	Arap3; Mir6981
3.29	0.0002	0.0447	Plxna2
3.28	0.0013	0.1443	Gm13772
3.28	0.0004	0.0622	Csf2rb2; Mir7676-1; Mir7676-2
3.27	0.004	0.2729	Rbp1
3.25	0.0292	0.6677	Ear12; Ear2; Ear3
3.25	0.0452	0.7664	Ptprb
3.22	1.26E-05	0.01	Cemip
3.21	0.0001	0.0351	Tagln
3.21	0.0373	0.7206	Cma1
3.21	0.0001	0.0389	Plbd1
3.2	0.0002	0.0422	Slc37a2
3.19	0.0293	0.6681	Slfn2
3.19	6.17E-05	0.0232	Spns2
3.18	0.0013	0.1443	Lmcd1
3.18	8.47E-05	0.0284	Cybb
3.17	0.0004	0.0636	Arhgap18
3.16	0.0038	0.2656	Mcoln2
3.16	1.04E-05	0.01	Hmga1-rs1
3.15	0.0298	0.6723	Eef1e1
3.14	0.0086	0.4022	Nid2
3.14	0.0015	0.1577	F11r
3.11	0.0009	0.1184	Ctsk
3.09	0.0003	0.0486	Gm14063; RP23-109J20.1
3.09	0.0159	0.5255	Marcks
3.08	0.0164	0.5324	Ldb2
3.07	0.0012	0.1394	Myd88
3.04	1.36E-05	0.01	Clec12a
3.04	0.0264	0.6423	Prcp
3.03	0.0005	0.0788	Clec4d
3.03	1.77E-05	0.0117	Lgi1
3.02	1.15E-05	0.01	Ecscr

3.01	0.0024	0.2042	Il1rn
3	0.0001	0.0351	Casp1
3	0.0022	0.1972	Gm11625
3	0.0282	0.6591	Il6st
2.99	1.34E-05	0.01	Tgfb1
2.98	0.0132	0.4901	Lbh
2.98	0.0146	0.507	Myh9
2.97	0.001	0.1187	Serpine1
2.97	0.0001	0.0356	Tubg1
2.96	3.93E-05	0.0204	Mcm5
2.96	0.0067	0.3642	Ctla2a
2.96	0.0202	0.5747	Ifi204
2.96	0.0033	0.2447	Tm4sf19
2.96	0.0007	0.0986	Eif2s1
2.95	0.0005	0.0795	Epha2
2.93	0.0136	0.4949	Gpr31b; Gpr31c
2.93	0.0006	0.09	Gsr
2.92	0.0159	0.5253	Gng11
2.92	0.007	0.37	Pak1
2.9	0.0124	0.4771	P2ry12
2.9	9.41E-05	0.0299	Plet1
2.89	0.006	0.3438	Il13ra1
2.89	0.0302	0.6754	Asb4
2.89	3.60E-06	0.0082	Wisp2
2.88	0.0003	0.0539	Cebpd
2.87	0.0024	0.2063	Ddx21
2.87	0.0005	0.0726	Casp8
2.87	0.0043	0.2825	Ece1
2.86	0.0019	0.1813	Cblb
2.85	0.0034	0.2494	Evi2a; Evi2b; Gm21975
2.84	0.0009	0.1179	Nr2f2
2.83	0.0118	0.4666	Lyz1
2.83	4.50E-05	0.0225	Tnfsf11
2.82	0.0471	0.7731	Sdpr
2.82	0.0003	0.0467	Icam1
2.8	0.0104	0.438	Gm13767
2.79	0.0002	0.0447	Adamts4
2.78	1.00E-05	0.01	Chil1

2.75	7.06E-06	0.01	Fscn1
2.75	0.0005	0.073	Hmox1
2.74	0.0283	0.6598	Fam43a
2.74	0.0119	0.4683	Ptprk
2.72	0.0074	0.3796	Myl9
2.71	0.016	0.5263	Pla2g7
2.71	1.41E-05	0.01	Slc9b2
2.7	0.0459	0.7675	Acp5
2.7	4.56E-05	0.0226	S1pr3
2.7	0.0168	0.538	Cmtm3
2.69	0.0029	0.2266	Cirh1a
2.69	0.0024	0.206	Rad9a
2.68	0.0013	0.1494	Olfr111
2.67	0.0053	0.3185	Mcts2
2.67	9.71E-05	0.0305	Dusp5
2.67	0.0049	0.3078	Fmo1
2.67	0.0056	0.3283	Penk
2.66	0.0014	0.1519	Cfl1
2.66	0.0087	0.4022	Dcstamp
2.66	0.0107	0.446	Larp4
2.66	0.0099	0.425	Map2k4
2.65	0.0103	0.4361	Cdkn2aipnl
2.65	0.0264	0.642	Gimap4
2.65	0.0004	0.0594	Lcp2
2.64	0.0163	0.5298	Dtx4
2.64	0.002	0.1841	Neurl3
2.64	0.0254	0.6326	Slc7a5
2.62	0.0113	0.4583	Haus6
2.61	0.0008	0.1045	Spry4
2.61	0.0008	0.1038	Gadd45g
2.6	0.0001	0.0364	Gpc1
2.6	0.0005	0.0795	Adam23
2.58	0.0281	0.6582	Gm7665
2.57	0.0312	0.6828	2900026A02Rik
2.56	0.0034	0.2487	Tm4sf1
2.56	0.0069	0.3684	Gm15428
2.55	0.0122	0.4738	Adssl1
2.55	1.15E-05	0.01	Tcirg1
2.55	0.0015	0.1594	Entpd1

2.54	0.003	0.2317	Nampt
2.54	0.0016	0.1621	Golm1
2.54	0.0031	0.2366	Actn1
2.53	0.0074	0.3796	Pik3cb
2.53	0.0007	0.0986	Tnfrsf21
2.53	0.0431	0.755	Nolc1
2.52	3.46E-05	0.0187	Plek
2.51	0.0024	0.2043	Gm14699
2.51	0.0047	0.2955	Nacc1
2.48	0.0219	0.5969	Adamts1
2.47	0.0266	0.6431	Arhgdib
2.47	0.0226	0.6032	Gm15899
2.46	0.0007	0.0956	Hcls1
2.46	0.0117	0.4656	Slc18a1
2.45	0.0005	0.0763	Gm14708; RP23-224M8.3
2.43	0.0116	0.4645	Mmp3
2.43	0.0025	0.207	Tlr7
2.43	0.0004	0.0639	Parvb
2.42	0.005	0.3104	Chrdl1
2.42	1.27E-05	0.01	Pitpnc1
2.41	0.0013	0.1478	Cyr61
2.41	0.0367	0.716	Clec4a3
2.4	0.0131	0.4879	Atp6v1c1
2.4	8.66E-06	0.01	Flt4
2.39	0.0198	0.5706	Havcr2
2.39	0.011	0.4515	Atp8b1
2.39	0.0203	0.5752	Cdh19
2.39	0.0425	0.7527	Ndst1
2.39	0.0053	0.3181	2810025M15Rik
2.39	0.0054	0.3217	Cbl
2.39	0.0248	0.6267	Tgfbr1
2.38	0.0076	0.3841	Lipa
2.38	0.0004	0.0617	Gm19505
2.38	0.0329	0.692	Ebf2
2.38	0.0454	0.7667	Il1b
2.38	0.0016	0.1624	Pum3
2.38	0.0348	0.7029	Pls3
2.38	0.0022	0.1942	Gm5762
2.38	0.0034	0.2502	Tmem161b
2.37	0.0004	0.0639	Tacr1

2.37	0.012	0.4708	Fads3
2.37	0.0005	0.0776	Ocstamp
2.37	0.0265	0.6423	Exoc6
2.37	1.06E-05	0.01	Schip1; Gm21949
2.37	0.0176	0.545	Ccnd1; Mir3962
2.37	0.0255	0.6335	Slc9a7
2.36	0.0037	0.2622	Prr5
2.36	0.0114	0.4605	Notch3
2.35	0.0189	0.5618	Sema6b
2.35	0.0088	0.4043	P2ry13
2.35	4.73E-05	0.023	Lat
2.34	0.0002	0.0414	Mafb
2.34	0.0091	0.4104	Lgi2
2.34	0.021	0.5851	Adamts5
2.34	0.0052	0.3157	Stab1
2.34	0.0001	0.0312	Selp
2.33	0.0391	0.7332	Dimt1
2.33	0.0079	0.3923	Hacd2
2.33	3.89E-05	0.0204	Gap43
2.33	0.0359	0.7088	Chchd3
2.32	0.0081	0.3985	Pbk
2.31	0.0398	0.7371	Slc9a9
2.31	0.0103	0.4358	Slit3
2.31	0.0032	0.2407	Angpt2
2.31	0.0401	0.739	Adgra2; Adgra3
2.3	0.0084	0.4022	Ifi202b; Ifi205
2.3	0.0121	0.472	Zfp946
2.3	0.0088	0.4038	Pdxk
2.29	0.033	0.6924	Rlbp1
2.29	0.0011	0.1277	Gm10087
2.29	7.27E-05	0.0255	Pcdh17
2.28	0.0382	0.7265	Snrpd3
2.28	0.0359	0.7088	Cd200
2.27	0.0014	0.1513	Sema6a
2.27	0.0287	0.6629	Zak
2.27	9.41E-05	0.0299	Il2rg
2.27	0.0133	0.4914	Casp4
2.26	0.001	0.1273	Actr3
2.26	0.0064	0.3551	Ndnf

2.26	0.0195	0.5673	Pira1
2.26	0.0002	0.0416	Abhd17c
2.25	0.0157	0.5237	Rgs16
2.25	0.0009	0.1182	ND2
2.25	0.0001	0.039	Ptpn6
2.25	0.0021	0.1896	Cluh
2.24	0.0018	0.1739	Bysl
2.24	3.74E-05	0.0199	Fermt3
2.24	3.02E-05	0.017	Ipo5
2.24	0.0012	0.1397	Gm13701; RP23-202M10.1
2.24	0.0018	0.1739	Timp3
2.23	0.002	0.1852	Tubb6
2.23	0.0019	0.1818	Fcgr1
2.23	0.0467	0.7716	Bmp5
2.23	0.0073	0.3775	Runx1
2.22	0.0021	0.1908	Abce1
2.22	0.0182	0.5542	Tjp1
2.2	0.0013	0.1443	Bmp2k
2.2	0.0036	0.2538	Ms4a6d
2.19	0.0141	0.5024	Prkar2b
2.18	0.0063	0.3514	Tbc1d8
2.18	1.44E-06	0.0058	Cd244
2.17	0.0004	0.0639	Klk10
2.17	0.0066	0.3628	Ugcg
2.17	0.0094	0.4174	Smap2
2.16	0.0003	0.0466	Wdr36
2.16	0.0049	0.3061	Tgm2
2.15	0.0079	0.3923	Ceacam1
2.15	0.0122	0.4738	Hexb
2.15	5.81E-05	0.0232	Coq3
2.15	0.0022	0.1966	Cct6a; Snora15
2.14	0.0041	0.2779	Nudt4
2.14	0.0033	0.2473	Angptl4
2.14	0.0006	0.0917	Tpm4
2.13	0.009	0.4061	Rasal2
2.13	0.0134	0.4925	Tpm1
2.13	0.0211	0.5858	Arrb2; Mir7115
2.13	5.44E-05	0.0232	Btk

2.12	1.08E-05	0.01	Map4k4
2.12	0.0324	0.6901	Phxr4
2.12	0.0109	0.4515	Gm12858
2.11	0.0012	0.1373	Zfp36
2.11	0.0321	0.6867	Rhod
2.11	2.19E-05	0.0136	Heatr1
2.11	0.0002	0.0437	Gm8822
2.11	1.86E-05	0.012	Rqcd1
2.1	0.0263	0.6416	Lrrc8b
2.1	0.0049	0.3076	Cenpe
2.1	0.0022	0.1972	Rlim
2.1	5.35E-06	0.01	Glipr1
2.1	4.87E-05	0.0232	Inpp5d
2.1	0.002	0.1856	Tes
2.09	0.0015	0.1596	Efhd2
2.08	0.0044	0.2857	Ctsb
2.08	0.0089	0.4061	Tmem173
2.08	0.0473	0.7736	Cxcr4
2.08	0.0343	0.7001	Lef1
2.08	8.73E-05	0.0287	Pilra
2.08	0.0462	0.7682	Nmd3
2.08	0.0019	0.1826	Fyb
2.08	0.0029	0.227	Ehd4
2.07	0.0003	0.0559	AF251705
2.07	0.044	0.7601	Mcm3
2.07	0.0124	0.4765	Actg-ps1; Gm23812
2.07	0.0364	0.7139	Hspa5
2.07	0.0393	0.7335	Usp31
2.06	0.0003	0.0549	Pde1b
2.06	0.0044	0.2848	Lum
2.06	0.0146	0.5072	Nol10
2.06	0.022	0.5986	Runx2
2.05	0.0029	0.229	Mapk11
2.05	0.0004	0.0639	Myct1
2.05	0.0011	0.1362	Cttnbp2nl
2.05	0.0015	0.1577	Apbb1ip
2.05	0.003	0.2332	Ccl9
2.05	0.0001	0.0385	Ttll12

2.04	0.0138	0.4985	Gucy1b3
2.04	0.0111	0.4537	S100a11
2.04	0.0257	0.6352	Ing5
2.04	0.0245	0.6247	Uchl5
2.04	0.0159	0.5258	Rgl1
2.04	9.59E-05	0.0303	Galnt10
2.04	0.015	0.5129	Pvr
2.04	0.0244	0.624	Cdk6
2.04	8.12E-06	0.01	Ptpre
2.03	0.0368	0.716	Gm10222
2.03	0.0111	0.4543	Sirpa
2.03	0.0004	0.0666	Tie1
2.03	0.0245	0.6247	Btg1
2.02	0.0005	0.0813	Cyth4
2.02	0.0242	0.6212	Cks1b
2.02	0.0423	0.7524	Slc43a3
2.02	0.0004	0.0622	Rsl1d1
2.01	0.0265	0.6423	Ms4a6c
2.01	0.0348	0.7028	Gars
2.01	0.0034	0.2496	Slc11a1
2.01	0.0013	0.1443	Etv6
2.01	0.0227	0.6041	Gm13252
2.01	0.0135	0.4929	Lyn
2.01	0.047	0.7731	Cyfip1
2.01	0.0042	0.2788	Zswim6
2	0.0127	0.4811	Slc38a4
2	0.0017	0.1647	Sh3bgrl3
2	0.0003	0.0575	Sorcs2
2	0.0015	0.1592	Ubap2
2	0.0014	0.1556	Acsl1
-2.01	0.049	0.781	Gm6954
-2.01	0.0365	0.7147	Mapk8ip1
-2.01	0.0085	0.4022	Dleu2; Mir16-1; Gm20034
-2.02	9.43E-05	0.0299	Glt8d1
-2.02	5.45E-05	0.0232	Plac9b; Plac9a
-2.02	0.0075	0.3826	Comp
-2.02	0.0187	0.5601	Sema5a
-2.03	0.0215	0.592	Fam150b
-2.03	0.0133	0.4902	Cyp39a1

-2.03	0.0068	0.3662	H2afv
-2.03	6.42E-05	0.0238	Ndn
-2.03	0.0352	0.7057	Rbp4
-2.03	0.0073	0.378	Fxyd1
-2.03	0.0032	0.2407	Mpnd
-2.03	0.0209	0.5833	Cask
-2.03	0.0155	0.519	Plxdc1
-2.03	0.0007	0.1007	Itpr2
-2.04	0.0065	0.3602	Irak1bp1
-2.04	0.0314	0.6839	Isoc1
-2.04	0.0384	0.7276	Alcam
-2.04	0.0205	0.5781	Mxra8
-2.05	0.0116	0.4645	Kdm3a
-2.05	0.0272	0.648	Rarres1
-2.05	0.0455	0.7667	Klf12
-2.05	0.0126	0.4779	Sox5
-2.05	0.0458	0.7675	Carf
-2.06	0.0007	0.0968	Tmem218
-2.06	0.0184	0.5574	Tcta
-2.06	0.0002	0.0414	Iqgap2
-2.07	0.0464	0.7694	Ogfod3
-2.07	0.0014	0.1508	Thsd4
-2.08	0.036	0.7097	Insl6
-2.08	0.0048	0.3006	Tcp11l2
-2.09	0.0011	0.1334	Plat
-2.09	0.0029	0.2267	Sash1
-2.09	0.0325	0.6903	Gm14569
-2.1	0.005	0.3101	4930523C07Rik
-2.1	0.0187	0.5601	Fut10
-2.11	0.0033	0.2458	S100a6
-2.11	0.0013	0.1438	9130023H24Rik
-2.11	0.0193	0.5666	Tgfbr3
-2.11	0.0004	0.0642	Rerg
-2.13	0.0455	0.7667	Stk38l
-2.14	0.0002	0.0447	Itih2
-2.14	0.0055	0.3257	Ltbp3
-2.14	0.0034	0.2494	Pappa
-2.15	0.0019	0.1769	Prdx4
-2.16	0.0093	0.4142	Rnf39
-2.16	0.0015	0.1566	Sept6
-2.16	0.0245	0.6247	Ttc26
-2.17	0.014	0.5015	Emp2

-2.17	0.0341	0.6992	Gm9830
-2.17	0.0012	0.141	Cox6b2
-2.18	0.0006	0.0834	Ackr2
-2.19	0.0004	0.067	Vsir
-2.21	0.0049	0.308	Desi2; Gm9982
-2.21	0.0009	0.1139	Rnf167
-2.21	0.0343	0.7001	S100a4
-2.23	0.0083	0.4022	Boc
-2.23	0.0024	0.2019	Gnpnat1
-2.24	0.0443	0.7614	Dpysl2
-2.25	0.0127	0.4812	Rabac1
-2.25	0.0463	0.769	Fam101b
-2.25	0.0169	0.5383	Thbs3
-2.26	0.0208	0.5819	Atp2b4; Mir6903
-2.26	0.0043	0.2823	Gm12697
-2.26	0.0012	0.1384	Gm14396; RP23-313J15.11
-2.27	0.0001	0.0364	Btc
-2.27	0.0222	0.5996	Alox12
-2.27	0.0185	0.5582	Ddx26b
-2.28	0.0252	0.6308	Psenen
-2.28	0.0451	0.766	Ltbp2
-2.28	0.0428	0.754	Triqk
-2.28	0.002	0.1863	Hspb8
-2.31	0.0094	0.4171	Tmem203
-2.31	0.0266	0.6431	Txndc15
-2.31	2.69E-05	0.0157	Six2
-2.31	0.0228	0.6049	Tmtc1
-2.32	0.002	0.1841	Thap3
-2.33	0.0007	0.0986	Rin2
-2.35	4.63E-05	0.0228	Fmod
-2.35	0.019	0.5628	Arntl
-2.36	0.0012	0.1373	Fam234a
-2.36	0.0387	0.7295	AF357426
-2.36	0.0017	0.1711	Ninj1
-2.37	0.0406	0.7409	Plek2
-2.38	0.0003	0.0495	Plac9b; Plac9a
-2.38	0.0023	0.1984	Emp3
-2.38	0.0079	0.3945	Gm6712
-2.39	0.0159	0.5253	Cachd1
-2.41	0.0458	0.7675	Zfp960
-2.42	0.0067	0.3657	Tppp3

-2.43	0.0199	0.572	1600002K03Rik
-2.43	0.0117	0.4656	Aga
-2.45	0.0134	0.4925	Kcnk6
-2.46	0.0081	0.3979	Itga10
-2.48	0.0334	0.6928	Zfp712
-2.48	0.0026	0.2089	Dnm1
-2.48	0.0227	0.6041	Robo1
-2.48	0.0063	0.3534	Gm6712
-2.49	0.0035	0.2512	Daam2
-2.53	0.0009	0.1184	Hmgn3
-2.54	0.0198	0.5705	Colec12
-2.54	0.0112	0.4574	Dock6
-2.55	0.0041	0.2779	Smpdl3a
-2.57	0.0294	0.6697	2010111I01Rik
-2.57	0.0005	0.0799	Bbs9
-2.58	0.0174	0.5449	Islr
-2.58	9.94E-06	0.01	Nupr1
-2.61	0.0041	0.2779	Tmem63a
-2.62	0.0083	0.4022	Plxdc2
-2.66	0.0184	0.5572	Nme5
-2.66	0.001	0.1243	Ggh
-2.69	0.0393	0.7335	Mmp2
-2.7	0.0002	0.0442	Sbsn
-2.73	0.0452	0.7664	Fam151b
-2.74	0.0192	0.5659	Adgrg2
-2.74	0.0234	0.6102	Fzd8
-2.75	8.73E-05	0.0287	Plac9b; Plac9a; Gm9780
-2.76	0.0006	0.0848	Barx1
-2.79	0.0001	0.0369	Selenbp1
-2.8	0.0069	0.3688	Slc27a6
-2.8	0.0021	0.1874	Npnt
-2.8	0.0199	0.571	Fap
-2.81	0.0166	0.5355	Cacna1g
-2.81	0.0017	0.1688	Fam129a
-2.83	0.0004	0.0606	Znrf3
-2.83	0.0008	0.1094	Sh3d19
-2.85	0.0186	0.5601	1810062G17Rik
-2.85	0.0239	0.616	Gsg1l
-2.86	0.0018	0.1731	Pgrmc1
-2.87	0.0002	0.0416	Nr1d1

-2.94	6.99E-05	0.025	Cc2d2a
-2.95	0.0014	0.1508	Gprc5a
-2.97	0.002	0.1863	Car5b
-2.97	0.0047	0.2993	Kcnma1
-3.04	0.0022	0.193	Rora
-3.09	0.003	0.2333	Sema3e
-3.14	0.0289	0.6648	Lrrn4cl
-3.16	0.0021	0.1875	Mamdc2
-3.16	0.0044	0.2869	Smoc1
-3.18	0.0305	0.6782	Slc9a3r1
-3.19	0.009	0.4071	1500009L16Rik
-3.24	0.0029	0.2261	Tbx4
-3.24	0.0085	0.4022	Vsig4
-3.33	0.0292	0.6677	Lipo1
-3.36	8.03E-05	0.0277	Ano1
-3.39	0.005	0.309	Tspan2
-3.43	0.0118	0.4677	Lipo2
-3.45	4.05E-05	0.0209	Selenbp2
-3.45	0.0055	0.3253	Fibin
-3.47	2.80E-06	0.0082	Ccdc109b
-3.54	8.20E-05	0.0281	Tspo
-3.54	8.19E-06	0.01	Cdon
-3.57	0.0139	0.499	Ptger3
-3.57	0.0404	0.7409	Pdgfrl
-3.61	6.90E-05	0.025	Spink2
-3.61	8.23E-05	0.0281	Nbl1
-3.64	0.0211	0.5869	Adamts16
-3.65	0.0108	0.4473	Aqp1
-3.67	0.0254	0.6326	Cdh13
-3.68	0.0264	0.642	Gm15378
-3.69	7.05E-05	0.025	Nrn1
-3.73	0.0023	0.2001	Ntn4
-3.74	0.0002	0.0447	Bmp4
-3.81	0.0008	0.1032	1500015O10Rik
-3.86	0.0047	0.2956	Crip1

-3.87	9.71E-06	0.01	Six1
-4.08	0.0012	0.1388	Prkd1
-4.18	0.0277	0.6531	Tmem100
-4.25	0.0002	0.0416	Ntrk3
-4.45	0.0008	0.1106	Nt5e
-4.56	0.021	0.5846	Ssc5d
-4.61	0.0025	0.2083	Garem
-5.13	0.0008	0.1027	Scara3
-5.15	0.0058	0.338	Rab37
-5.15	0.0445	0.7623	Matn2
-5.18	0.0169	0.5383	Igsf10
-5.18	0.0096	0.4198	Sema3c
-5.19	0.0154	0.5185	Plpp3
-5.35	0.017	0.5408	Lyve1
-5.47	0.002	0.1863	Sulf2
-5.53	0.0432	0.7552	Fgl2
-5.57	0.0015	0.1594	Dlx3
-5.96	0.0137	0.4955	Dkk3
-6.02	0.0469	0.773	Htra1
-6.12	2.35E-05	0.014	Kazald1
-6.28	0.0079	0.3923	Itih5
-6.83	0.0025	0.2073	Rgcc
-6.98	0.0068	0.3668	Hhip
-7.37	0.0003	0.0516	Dcx
-7.72	0.0009	0.1184	Ephx1
-7.91	0.0012	0.1413	Hbegf
-8.72	1.65E-06	0.0058	Angptl1
-8.85	0.0002	0.0447	Osr2
-8.9	0.0214	0.5906	Mir376c
-9.22	0.0025	0.207	Stc1
-9.56	0.0024	0.2062	Mir677
-9.87	3.45E-05	0.0187	Gdf10
-10.46	0.044	0.7601	Anxa8
-11.32	6.68E-05	0.0245	Vit
-12.76	9.00E-07	0.0045	Ecm2
-12.92	0.0029	0.2273	Hoxd10
-13.15	4.63E-07	0.0033	Spon2

-17.18	1.44E-05	0.01	Sema3d
-20.05	0.0003	0.0493	Casr
-20.1	1.19E-05	0.01	Creb5; 9430076C15Rik
-22.17	0.0009	0.1161	Sema3a
-25.64	0.0007	0.1008	Wif1
-26.34	1.52E-05	0.0102	Calb2
-30.43	0.0007	0.0965	Egfl6
-34.4	0.0002	0.0391	Tspan15
-37.95	9.12E-06	0.01	Cilp
-59.86	0.0024	0.2035	Clic5
-137.39	0.0004	0.0676	Thbs4
-174.88	1.86E-06	0.0058	Htra4
-696.63	0.0005	0.0788	Prg4

Table S5 Signaling pathways differentially expressed in the canal versus the periarticular region.

Pathway	Gene		Fold Change
EGFR	*Btc*	betacellulin	-2.27
	Cbl	Casitas B-lineage lymphoma	2.39
	Cblb	Casitas B-lineage lymphoma b	2.86
	Ceacam1	carcinoembryonic antigen-related cell adhesion molecule 1	2.15
	Dnm1	dynamin 1	-2.48
	Hbegf	heparin-binding EGF-like growth factor	-7.91
	Pak1	p21 protein (Cdc42/Rac)-activated kinase 1	2.92
	Pik3cb	phosphatidylinositol 3-kinase, catalytic, beta polypeptide	2.53
	Ptk2b	PTK2 protein tyrosine kinase 2 beta	3.81
	Ptpn6	protein tyrosine phosphatase, non-receptor type 6	2.25
	Rgs16	regulator of G-protein signaling 16	2.25
Semaphorin	*Nrp1*	neuropilin 1	4.6
	Nrp2	neuropilin 2	3.59
	Plxdc1	plexin domain containing 1	-2.03
	Plxdc2	plexin domain containing 2	-2.62

	Plxna2	plexin A2	3.29
	Plxnd1	plexin D1	10.8
	Sema3a	semaphorin 3A	-22.17
	Sema3c	semaphorin 3C	-5.18
	Sema3d	semaphorin 3D	-17.18
	Sema3e	semaphorin 3E	-3.09
	Sema5a	semaphorin 5A	-2.02
	Sema6a	semaphorin 6A	2.27
	Sema6b	semaphorin 6B	2.35
	Sema7a	semaphorin 7A	7.91
TGFβ	*Bmp4*	bone morphogenetic protein 4	-3.74
	Lef1	lymphoid enhancer binding factor 1	2.08
	Runx2	runt related transcription factor 2	2.06
	Serpine1	serine (or cysteine) peptidase inhibitor, clade E, member 1	2.97
	Spp1	secreted phosphoprotein 1	58.6
	Tgfb1	transforming growth factor, beta 1	2.99
	Tgfbr1	transforming growth factor, beta receptor I	2.39
	Tgfbr3	transforming growth factor, beta receptor III	-2.11
Wnt	*Arrb2*	arrestin, beta 2	2.13
	Ccnd1	cyclin D1	2.37
	Dkk3	dickkopf homolog 3	-5.96
	Fzd4	frizzled homolog 4	3.87
	Fzd8	frizzled homolog 8	-2.74
	Lef1	lymphoid enhancer binding factor 1	2.08
	Mapk8ip1	mitogen-activated protein kinase 8 interacting protein 1	-2.01
	Prkd1	protein kinase D1	-4.08
	Runx2	runt related transcription factor 2	2.06
	Wif1	Wnt inhibitory factor 1	-25.64
	Wisp2	WNT1 inducible signaling pathway protein 2	2.89
Delta/Notch	*Dtx4*	deltex 4 homolog	2.64
	Hey1	hairy/enhancer-of-split related with YRPW motif 1	3.48
	Jag1	jagged 1	3.95
	Lef1	lymphoid enhancer binding factor 1	2.08
	Notch3	notch 3	2.36
	Pak1	p21 protein (Cdc42/Rac)-activated kinase 1	2.92

Graphical Abstract **Schematic of SOC canal formation.** SOC development is initiated by invasion of periarticular, multipotent mesenchymal progenitors from discrete sites along the epiphyseal surface into the underlying cartilage (i). At the time of SOC initiation, these periarticular cells, but not surrounding chondrocytes, express VEGF, important for recruiting individual endothelial cells (vasculogenesis) and existing vessels (angiogenesis) from the surrounding vasculature (ii). Invasion of the SOC canal is associated with extensive proliferation within the canal, degradation of chondrocyte matrix and chondrocyte apoptosis. Transition from canal invasion to expansion is associated with a redistribution of VEGF expression, from cells within the canal and along the leading edge, to surrounding hypertrophic chondrocytes (iii). This transition is associated with a transformation from periarticular cell-led invasion to blood vessel-led SOC expansion. SOC expansion continues, eventually giving rise to the epiphyseal marrow cavity (iv). Mesenchymal lineage cells (ie. osteoblasts, osteocytes, perivascular cells, etc.) within the epiphyseal region are derive from periarticular progenitor cells present within the invading SOC canal.

Graphical Abstract