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Lymph node mesenchymal and endothelial stromal cells cooperate via the RANK-

RANKL cytokine axis to shape the sinusoidal macrophage niche

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Summary

Tissue-resident macrophages are receptive to specific signals concentrated in cellular niches that direct their cell differentiation and maintenance genetic programs. Here we found that deficiency of the cytokine RANKL in lymphoid tissue organizers and marginal reticular stromal cells of lymph nodes resulted in the loss of the CD169+ sinusoidal macrophages (SMs) comprising the subcapsular and the medullary subtypes. Subcapsular SM differentiation was impaired in mice with targeted RANK deficiency in SMs. Temporally controlled RANK-removal in lymphatic endothelial cells (LECs) revealed that lymphatic RANK activation during embryogenesis and shortly after birth was required for the differentiation of both SM subtypes. Moreover, RANK expression by LECs was necessary for SM restoration following inflammation-induced cell loss. Thus, cooperation between mesenchymal cells and LECs shapes a niche environment that supports SM differentiation and reconstitution after inflammation.

Introduction

Lymphoid tissues comprise mesenchymal and endothelial stromal cells. They play a key role in the development of secondary lymphoid organs such as lymph nodes (LNs) (Onder and Ludewig, 2018; van de Pavert and Mebius, 2010) and function in the compartmentalization of B cell and T cell zones, antigen transport and immune regulation (Buechler and Turley, 2018). Recently, an increasing diversity of mesenchymal stromal cells has emerged (Huang et al., 2018; Rodda et al., 2018; Takeuchi et al., 2018), among which the marginal reticular cells (MRCs). They reside in the LN marginal area between the subcapsular sinus and the B cell follicles and are characterized by the expression of the TNFSF member RANKL (TNFSF11) (Katakai et al., 2008; Rodda et al., 2018). RANKL is known for the differentiation of osteoclasts, specialized bone-resorbing macrophages (Dougall et al., 1999; Kong et al., 1999; Walsh and Choi, 2014), but is also required for LN organogenesis since mice deficient for RANKL or its signaling receptor RANK (receptor activator of NF-κB, TNFRSF11a) lack all LNs (Dougall et al., 1999; Kim et al., 2000; Kong et al., 1999). In the embryonic LN anlagen, RANKL is expressed by the stromal lymphoid tissue organizers (LTOs) and lymphoid tissue inducer (LTi) cells (Cupedo et al., 2004; Sugiyama et al., 2012), and it has recently been shown that RANK expression by lymphatic endothelial cells (LECs) is necessary for LN organogenesis (Onder et al., 2017). However, the function of stromal RANKL in LN development and function remains incompletely understood. We have recently observed that stromal RANKL activates LECs to express ITGA2b suggesting that a cross-talk between these two cell types could affect immune function (Cordeiro et al., 2016).

Macrophages that line the lymphatic sinuses of LNs comprise the CD169⁺ subcapsular sinusoidal macrophages (SSMs), localized between the B cell follicles and the subcapsular sinus, and the CD169⁺ SIGN-R1⁺ medullary sinusoidal macrophages (MSMs) associated with the medullary lymphatics. Both populations play an important role in the initiation and the regulation of innate and adaptive immunity (Gray and Cyster, 2012). In response to viral pathogens, SSMs produce IFN-I that protects neighboring cells (lannacone et al., 2010; Moseman et al., 2012) or activate the inflammasome that fuels the immune response (Sagoo et al., 2016). SSMs also transfer lymph-borne antigens to B cells that relay it to the stromal follicular dendritic cells for an efficient secondary immune response (Carrasco and Batista, 2007; Phan et al., 2007). MSMs also contribute to the immune response by the release of inflammatory mediators (Chatziandreou et al., 2017).

Tissue macrophages derive from yolk sac macrophages and fetal liver monocytes, or in the adult from bone marrow-derived monocytes (Ginhoux and Guilliams, 2016). Lineage-

determining transcription factors provide a core macrophage development program, and tissue-derived signals oversee the final differentiation refinement (Lavin et al., 2015; T'Jonck et al., 2018). Macrophage precursors can receive secondary signals that are unique to each particular cell niche through cell-cell contacts and soluble factors (Guilliams and Scott, 2017). It ensures that the macrophages are well adapted to their local environment. SMs require CSFR-1 signals (Witmer-Pack et al., 1993), but in addition SSM differentiation is dependent on lymphotoxin $\alpha\beta$ (LT) produced by the adjacent B cells (Moseman et al., 2012; Phan et al., 2009).

Here we examined the role of RANKL expressed by the mesenchymal LTO and MRC stromal cells in the LN. We found that *Ccl19* promoter-directed RANKL ablation in LTOs and MRCs did not significantly affect LN organogenesis but resulted in the specific loss of SMs. Deficiency in RANK, the signaling receptor of RANKL, affected SSMs directly as these cells were absent in *Cd169-cre Rank*^{fl/fl} mice. However, deletion of RANK in LECs during mouse embryogenesis or in the first weeks after birth resulted in the loss of both SM subsets. RANK activation of LECs was also required for SM-network restoration after an inflammatory insult. Inactivation of RANK signaling in LECs correlated with the reduced presence of CD11b⁺ precursors in embryos and adult mice, supporting a role for this axis in cell recruitment or retention. As a result, the absence of stromal RANKL or lymphatic RANK compromised the immune response to a viral pathogen. Taken together, our findings show that this mesenchymal – endothelial cell interaction shapes a niche environment that is mandatory for SM differentiation during development and for reconstitution after inflammation.

Results

RANKL is specifically deleted in LTOs and MRCs without affecting MRC differentiation

CCL19 is expressed in lymphoid tissue organizers (LTOs) (Benezech et al., 2011; Chai et al., 2013) that are presumed to give rise to the MRCs, the main constitutive source of RANKL in the adult LN (Katakai, 2012; Rodda et al., 2018). Therefore, to address the function of stromal RANKL, we crossed *Rankl*^{fl/fl} mice (Xiong et al., 2011) with mice expressing the cre recombinase under control of the *Ccl19* promoter (Chai et al., 2013). Microscopic inspection of embryonic E17.5 inguinal LNs of *Ccl19*-cre *Rankl*^{fl/fl} mice (denoted as *Rankl*^{4Ccl19}) revealed a markedly diminished expression of RANKL by the LTOs (**Figure 1A**). At this age, LTi cells express little RANKL (Sugiyama et al., 2012). LECs, identified by mCLCA1 (Furuya et al., 2010), and the presence of mature LTi cells expressing CD4 appeared normal. The mice developed all LNs with little alteration in cellularity and cell composition (**Figure S1A,B**), which is in contrast to

unconditional RANKL-deficient mice that lack all LNs (Kong et al., 1999). In agreement with a direct lineage relationship between LTOs and MRCs (Takeuchi et al., 2018), the expression of RANKL was no longer observed in MRCs of adult Rankl^{ACC/19} mice (Figure 1B). To determine whether the disappearance of RANKL altered MRC differentiation, we identified MRCs among the gp38⁺ CD31⁻ stromal fibroblastic reticular cells (FRCs) based on the expression of MAdCAM-1 and VCAM-1 (Hoorweg et al., 2015; Katakai et al., 2008) (Figure 1C). The proportion of MRCs was not altered in the RANKL-mutant mice (Figure 1D). Moreover, when Rankl^{ACC/19} mice were crossed with tdTomato reporter mice, red fluorescent stromal cells were found between the follicular dendritic cells and the subcapsular sinus, indicative of correctly positioned MRCs (Figure S1C). TdTomato⁺ T cell zone-residing reticular cells (TRCs) were also observed, suggesting that the lack of RANKL has no effect on other stromal subsets. We determined Rankl gene expression by RT-qPCR in sorted MRCs and in the remaining stroma of Rankl^{ACcl19} and control Rankl^{fl/fl} mice. Figure 1E shows that MRCs transcribed Rankl, and, as expected, there was a clear reduction in the number of transcripts in MRCs from *Rankl^{ACC/19}*mice. Taken together, the chosen gene-targeting strategy established a reliable mouse model for Rankl deletion from the mesenchymal LN stromal cells.

Stromal RANKL is required for SM differentiation

In the light of the expression of RANK by the myeloid lineage in response to CSF-1 (Arai et al., 2012), alongside its role in osteoclastogenesis (Dougall et al., 1999), we asked whether the loss of stromal RANKL had an impact on macrophage differentiation in the LN. We first focused on the subcapsular sinusoidal macrophages (SSMs) because these cells reside in the same zone as the MRCs. SSMs express CD169, and staining LN sections for CD169 uncovered that this marker was markedly diminished in *Rankl^{ACcl19}* mice (Figure 2A). Since CD169 expression in wild-type mice is lower in the medullary area, we also stained for SIGN-R1, expressed by the medullary sinus macrophages (MSMs) but not by the SSMs (Moseman et al., 2012). There was a clear reduction in the extent of SIGN-R1 and CD11b staining, but the formation and the position of the B220⁺ B cell follicles appeared normal (**Figure 2A**). To quantify a decline in these two macrophage subsets, and to assess other myeloid cell populations, we performed analyses by flow cytometry. Among live CD11b⁺ CD11c⁺ cells, SSMs and MSMs were MHC-II⁺ CD11c^{low} and could be distinguished as CD169⁺ F4/80⁻ and CD169⁺ F4/80⁺ cells, respectively (**Figure 2B**). We found that the numbers of SSMs and MSMs were significantly reduced in the mutant mice (Figure 2B). In contrast, the F4/80 single-positive macrophages were slightly increased, and the remaining double-negative macrophages, that likely comprise the T cell zone macrophages

(Baratin et al., 2017), were not affected (**Figure 2C**). We found no alteration in the numbers of the tissue-derived CD11c⁺ CD11b⁺ MHC-II^{hi} DCs, or the LN-resident CD11c⁺ CD11b⁺ MHC-II⁺ DCs (**Figure 2D**). Thus, stromal RANKL is specifically required for the differentiation of the subcapsular and the medullary SM subsets.

Impaired immune response in stromal RANKL-deficient mice

SMs relay lymph-borne antigen to B cells (Phan et al., 2007) and stimulate the immune response to viral pathogens (Chatziandreou et al., 2017; Gaya et al., 2015; Sagoo et al., 2016). Therefore, to ascertain that their diminished number in Rankl^{ACcl19} mice has functional implications, we first tested the relay of immune complexes to B cells. To this end, we passively immunized Rankl^{ACC/19} or Rankl^{f//fl} mice with anti-phycoerythrin (PE) antibodies and then administered PE into the hind footpad (Phan et al., 2007). Eight hours later, popliteal LNs were processed to harvest B cells. The addition of CD45.1⁺ lymphocytes from the Ly5.1 congenic strain to the cell suspension allowed to distinguish between in vivo PE-uptake and PEacquisition during cell preparation. B cells from CD45.2 Rankl^{4Ccl19} or Rankl^{fl/fl} mice were identified and analyzed by flow cytometry. Indeed, the proportion of PE^+ CD45.2 B cells was significantly lower in the conditional RANKL-deficient mice (Figure 3A). Next, we tested the infection with the vesicular stomatitis virus (VSV), known to target SSMs (lannacone et al., 2010; Junt et al., 2007). RANKL-deficient and control mice received an intra footpad (i.fp.) administration of 10⁶ pfu VSV, and 6h later the popliteal LNs were imaged for VSV replication using the anti-VSV-glycoprotein antibody Vi10 (Honke et al., 2011). While VSV infection of CD169⁺ SSMs was clearly detected in the control mice, there was a significant drop in infection of Rankl^{ACcl19} mice (Figure 3B). Both SM subsets have been implicated in the immune response against Modified Vaccinia Ankara (MVA) virus (Chatziandreou et al., 2017; Gaya et al., 2015; Sagoo et al., 2016). Therefore, the mice received an i.fp. administration of 10⁴ pfu of MVA virus, and, 7 days later, the formation of germinal center B cells and plasma cells was assessed by flow cytometry. In spite of an increase in general cellularity, indicative of an ongoing immune response (**Figure 3C**), the capacity of the mutant mice to generate GL-7⁺ Fas⁺ germinal center and CD138⁺ plasma B cells was abolished in the RANKL-mutant mice (**Figure 3D**). Taken together, the results demonstrate that stromal RANKL is a critical component for the response to viral infection by providing the signal required for SM differentiation.

SSMs are dependent on direct RANK-signaling

To address the mechanism underlying the RANKL-mediated SM differentiation, we reasoned that the cell differentiation program could be directly instructed by RANKL and sought to genetically deplete Rank from SMs. Both SM subsets transcribe Rank, albeit less then LECs (Figure S2A). However, a gene targeting strategy in the myeloid lineage using Cd11c ($Itg\alpha x$)-cre or LysM (Lyz2)-cre mice crossed with Rank^{fl/fl} mice (Rios et al., 2016) had no effect on the SMs (Figure S2B). Because these promoters are poorly active in SMs (Gaya et al., 2015), we next chose the Cd169-cre mouse, which faithfully transcribes the cre recombinase from within the Cd169 gene without affecting protein expression (Karasawa et al., 2015). When crossed with tdTomato reporter mice, red fluorescence was indeed restricted to the SM compartment (Figure S2C). We therefore generated Cd169-cre Rank^{fl/fl} (Rank^{ΔCd169}) mice. Immunolabeling of LN sections for CD169 uncovered a conspicuous absence in the subcapsular area, however, its expression was maintained in the medulla (Figure 4A). Indeed, the staining for SIGN-R1 revealed a normal presence of MSMs. Moreover, SIGN-R1⁺ cells were also discernable in the subcapsular area, lining the B cell follicle. This suggests a deregulation of SSM differentiation, which is reminiscent of the effect of LTbR-inhibition (Moseman et al., 2012). Quantification of the SM cell numbers in *Rank*^{ACd169} and control mice using the previous flow cytometry strategy confirmed a reduction of the SSM population (Figure 4B). There were no significant alterations in the numbers of the other macrophage subtypes, the LN-resident DCs or the migratory DCs (Figure S2D-F). To address the possibility that the normal presence of MSMs was due to inefficient cre-mediated Rank gene recombination, both SM subsets were sorted from Cd169cre Rank^{fl/+} heterozygous mice and gene recombination verified by PCR on genomic DNA. However, the expected *Rank* exon deletion occurred in both cell types (Figure S2G). We next treated adult wild-type mice with RANKL-neutralizing antibody (Kamijo et al., 2006) and, as controls, either LTb receptor (R)-Fc fusion protein or TNFR2-Fc (Etanercept). Three weeks later, the numbers of SMs were determined. RANKL-blocking antibody, LTbR-Fc (Moseman et al., 2012; Phan et al., 2009) but not TNFR2-Fc (Ettinger et al., 1998) significantly diminished SSM numbers, while the medullary counterpart was unchanged (Figure 4C). Taken together, the data are in support of a requirement of direct RANK engagement for maintenance of SSMs.

To address the question whether SSMs are dependent on RANK for cell viability, as has been proposed for DCs (Josien et al., 2000), we irradiated adult *Rank*^{ΔCd169} and control mice while shielding the brachial LNs. Bone marrow cells from wild-type Ly5.1 mice were then adoptively transferred. Four weeks later, the proportion and the cell numbers of CD45.1⁺ donor and CD45.2⁺ recipient SSMs and MSMs in the protected LNs were determined. A more pronounced replacement of the RANK-deficient SSMs by donor cells should be expected in the case of a reduced life span, however, the proportion of donor versus recipient SSMs was not different between genetically-modified and control mice (**Figure S3A**). Moreover, the numbers of SSMs remained low in the *Rank*^{Δ Cd169} mice despite the fact that the donor SSMs expressed RANK. This is in accord with the observation that the SSM niche is occupied by CD11b⁺ SIGN-R1⁺ CD169⁻ cells thereby limiting the expansion of RANK-sufficient CD45.1⁺ macrophages.

We next determined whether the loss of RANK under *Cd169* gene control affected macrophages of the liver, lung or the splenic red pulp, given the expression of RANK or CD169 by macrophages in these tissues (Chow et al., 2013; Mass et al., 2016). The Kupffer cells, the alveolar macrophages and the splenic red pulp macrophages were identified using established cell isolation and flow cytometry methods (Scott et al., 2018). Yet, no significant difference in proportion or numbers was observed between *Rank*^{*ACd169}</sup> and control mice* (**Figure S3B-D**). Taken together, RANKL provides mandatory signals for the LN SSM subset, most likely by directly regulating their cell differentiation and maintenance.</sup>

The formation of the SM niche during development is instructed by RANK-activated LECs

Because direct activation only partially accounts for the loss of SMs in Rankl^{ACc/19} mice, we asked whether the macrophages would be sensitive to a RANKL-stimulated cellular microenvironment. We have previously shown that LECs express MAdCAM-1 and ITGA2b in response to RANKL (Cordeiro et al., 2016) and that RANK expression by LECs is required for LN formation (Onder et al., 2017). Therefore, we crossed the Rank^{fl/fl} mice with Prox1-cre^{ERT2} mice, which express a tamoxifen-inducible cre recombinase specifically in LECs (Bazigou et al., 2011). Tamoxifen delivery to Prox1-cre^{ERT2}Rank^{fl/fl} (Rank^{$\Delta Prox1$}) mice resulted in the expected gene segment excision in LECs, but not in blood endothelial cells (BECs) nor in FRCs (Figure S4A). We administered tamoxifen to 4 week-old $Rank^{\Delta Prox1}$ mice or to their $Rank^{fl/fl}$ littermates and then every 2 weeks for 8 weeks. Immunofluorescence staining showed that MAdCAM-1 expression by LECs was abolished (Figure 5A), which was validated by flow cytometry (Figure S4B), yet the MRCs were still present (Figure S4C). Immunolabelling and flow cytometry analysis of the SSMs and MSMs revealed that both subsets were normal in position and numbers (Figure 5A). Because low cell turnover rate and/or already differentiated SMs may render the cells insensitive to the absence of LEC-delivered signals, we hypothesized that Rank excision may have more impact when triggered earlier. Therefore, we delivered tamoxifen to 2 week-old mice and then every 2 weeks. Indeed, this resulted in a marked reduction in CD169 and SIGN-R1 expression and a significant loss of SSM and MSM cell numbers (Figures 5B). In contrast,

the other macrophage populations, dendritic cells, B and T cells were unaffected (Figure SSA-C). Finally, we administered tamoxifen to pregnant dams to target E18.5 embryos. This procedure resulted in the absence of CD169 and an almost complete loss of SIGN-R1 (Figure SC). As expected (Onder et al., 2017), embryonic *Rank* deletion in LECs also negatively affected organ size. However, intra-gastric tamoxifen delivery to P1-P4 newborns had a reduced impact on organ size and allowed a more accurate assessment of SM numbers; it confirmed the reduction of both sinusoidal subsets (Figure SD). To verify that SMs are already present in the embryonic LNs, we stained E17.5 LN anlagen for CD169, together with CD4 and LYVE-1 for LTi cells and LECs, respectively. CD169⁺ cells were detected at this age and were found closely associated with the LECs (Figure SSD). Although some macrophages may express LYVE-1, these embryonic CD169⁺ macrophages appeared to lack this marker. Instead, LYVE-1 was evenly distributed throughout the LECs at this age (Bovay et al., 2018). At postnatal day 6, SSMs and MSMs had taken residence in their distinctive anatomical sites and their numbers increased with age (Figure SSE). These data demonstrate that RANK-activated LECs function in the formation of the SM compartment during late embryogenesis and early post-natal life.

Reconstitution of the SM network relies on RANK-activated LECs

The findings agree with the model of a cooperation of LECs with the RANKL-expressing mesenchymal cells to constitute a microenvironmental niche tailored for SMs when their precursors take up residence in the embryonic LN anlagen. We next asked whether the niche activation would again be required to reconstitute the macrophage population after its integrity has been disrupted. It has been shown that SMs vanish in response to innate immune stimuli, which provided a means to test this possibility (Chatziandreou et al., 2017; Gaya et al., 2015; Sagoo et al., 2016). In response to an i.fp. injection of Toll-like receptor 9 (TLR9) agonist CpG, but not PBS, the CD169⁺ SSMs and the CD169⁺ SIGN-R1⁺ MSMs were undetectable after 4 days, in spite of a massive recruitment of CD11b⁺ cells (Figure 6A). Yet, 4 weeks later, when inflammation had receded, the SM compartment had normalized. This procedure was repeated in $Rank^{\Delta Prox1}$ and $Rank^{fl/fl}$ mice with tamoxifen delivered 5 days post-CpG and renewed every 2 weeks. We observed by immunofluorescence and flow cytometry that while in Rank^{fl/fl} controls both subsets had reconstituted within 5 weeks, SM restoration was incomplete in Rank^{AProx1} mice (Figure 6B and 6C). To confirm these findings in the context of a relevant immune response, the procedure was repeated and MVA was i.fp. administered at 5 weeks. Seven days later the cell proportions and the numbers of germinal center B cells and plasma cells were measured. The silencing of RANK expression after CpG-induced SM loss perturbed the normal formation of germinal center B cells and plasma cells (**Figure 6D**). Therefore, LEC activation by RANKL is required to reconstitute the niche environment for SM restoration after network disruption by innate immune stimuli.

Impaired SM niche constitution correlates with fewer CD11b⁺ cells

To obtain an insight into the downstream pathways induced by RANK signaling in LECs, we performed RNA-sequencing of LECs purified from Rankl^{ACcl19} and control mice. In addition to the diminished gene expression of Madcam-1 and Itga2b, we observed reduced Ccl20 and increased Ackr4/Ccrl1 transcription (Figure 7A). These variation in gene expression were validated by RT-qPCR in LECs purified from Rank^{AProx1} and control littermates (Figure 7B). A downstream pathway analysis uncovered, among others, chemotaxis and myeloid cell differentiation (Figure S6). We next determined whether RANK-activation of LECs translated into an increased recruitment/retention of potential myeloid precursor cells. The immunofluorescence analysis of LN sections of Rank^{AProx1} mice 5 weeks after CpG stimulation and tamoxifen treatment showed a discernable deficiency in CD11b⁺ cells in the subcapsular and medullary sinusoidal areas (**Figure 7C,D**). A reduction in CD11b⁺ cells was confirmed by flow cytometry (Figure 7E). This supports a role of RANK-activated LECs in the recruitment and/or the retention of myeloid cells that would subsequently give rise to SSMs and MSMs. To explore this notion further, we asked whether RANK deficiency in LECs would likewise result in diminished numbers of CD11b⁺ cells in the embryonic LN. Tamoxifen was delivered to pregnant dams at the embryonic age of E11.5 and E12.5 when LTi cells populate the developing LN (Bovay et al., 2018; Onder et al., 2017). Whole mounts of E17.5 inguinal LN anlagen were stained for CD11b alongside smooth muscle actin (SMA) to mark vascular smooth muscle cells around major blood vessels and LYVE-1 for lymphatics. CD11b⁺ embryonic macrophages were present in control LN anlagen, however they were significantly reduced in embryos with LECspecific Rank deletion (Figure 7F,G). These findings show that RANK-activated LECs increase the numbers of LN CD11b⁺ cells that may function as SM precursors during embryonic development and in inflammatory situations in the adult.

Discussion

Secondary lymphoid organs comprise different stromal cells that map to distinct anatomical locations. They interact directly with immune cells to compartmentalize and regulate the immune response. Here we demonstrated that mesenchymal stromal cells, through RANK-RANKL signaling, created a niche environment with LECs for specialized macrophages to take

up residence, complete their differentiation program and fulfill their immune function. Mice deficient in stromal RANKL showed reduced numbers of SSMs and MSMs and, as a consequence, were compromised in antigen-transport to B cells, viral infection and the antiviral immune response. The absence of SSMs in mice with RANK deficiency in CD169⁺ cells and after RANKL-neutralization demonstrated that SSMs were dependent on direct and continuous RANKL stimulation. Moreover, RANK activation of LECs was mandatory during development and after inflammation for the formation of both SM subtypes. Finally, the data suggest that activated LECs contribute to the SM compartment by regulating the presence of myeloid cell precursors.

RANKL is expressed by the mesenchymal LTOs in the embryonic LN anlagen and by the MRCs in the adult LNs (Katakai, 2012; Sugiyama et al., 2012). To address the function of stromal RANKL in lymphoid tissue, we made use of the Ccl19-cre mice that allows genetic ablation in LTOs and in the mesenchymal cells of most adult secondary lymphoid organs (Chai et al., 2013). Using this strategy, the removal of RANKL from LTOs and MRCs did not markedly affect LN organogenesis except for a slightly reduced inguinal LN size. This is in contrast to the effect of RANK silencing in LECs that resulted in a smaller organ even when deleted late in embryogenesis at E18.5. Because at this stage in development LTi cells express little RANKL (Sugiyama et al., 2012), it may be supplemented from other cellular sources. For instance, we and others have shown that soluble RANKL is produced by the embryonic/newborn skin and can reach the draining LN (Duheron et al., 2011; Kartsogiannis et al., 1999). Alternatively, it is not excluded that stromal RANKL deletion is insufficient or belated, as, indeed, residual stromal RANKL was observed at E17.5 before a complete shut-down in the adult. The low RANKL expression sufficed to support the ongoing organogenesis, but could not complete the installation of the SM populations. We found a marked reduction in the SM compartment, SSMs and MSMs being both profoundly impacted in the *Rankl^{ACc/19}* mice. This finding was based on the expression of the key markers for these cells (CD169 expressed exclusively by both subsets and SIGN-R1 restricted to the MSMs), as well as impaired function. Mice lacking stromal RANKL showed diminished immune complex transfer to B cells, normally ensured by SSMs (Phan et al., 2007), impaired infection with the SSM-targeting VSV (lannacone et al., 2010; Junt et al., 2007), and a failure to mount an SM-dependent immune response to MVA (Chatziandreou et al., 2017; Gaya et al., 2015; Sagoo et al., 2016).

We uncovered two underlying mechanism for stromal RANKL dependence of SMs. First, SSMs required direct RANK signaling, second, both subsets relied on RANK-activated LECs. By silencing RANK expression in the SM compartment using *Cd169-cre* mice, we observed a reduction in CD169 expression and aberrant expression of SIGN-R1 by CD11b⁺ cells of the subcapsular zone. This indicates that RANK-deficient macrophages can take residence in this zone but are unable to complete their differentiation program. The absence of restoration of the SSM population by donor-derived RANK-sufficient precursors after a partial irradiation supports the occupation of the niche by other cells. The unchanged renewal rate makes the possibility that RANK conveys cell survival or proliferative signals unlikely. A similar phenotypic change is observed when LTbR signaling is blocked by LTbR-Fc resulting in the presence of SIGN-R1⁺ cells in place of SSMs (Moseman et al., 2012). All things considered, the data support the idea that RANK directly activates a differentiation program that also requires LTbR signaling. Because RANK and LTbR activate unique and overlapping cell signaling pathways (Remouchamps et al., 2011; Walsh and Choi, 2014) it is conceivable that both receptor transduction pathways cooperate to direct SSM differentiation. Yet, conclusive confirmation for this model awaits in vitro differentiation experiments.

The nature of a secondary differentiation signal used by MSMs remains open to conjecture. Given that F4/80 is frequently found on different types of tissue macrophages, it is possible that a co-stimulus may not play an important role for MSMs, and that this cell type rather reflects a default program arising in the absence of continuous RANK-engagement. Indeed, because MSMs transcribed *Rank*, and gene recombination occurred in MSMs of *Cd169-cre* mice, the simplest explanation would be that RANK is not engaged in these cells because of insufficient RANKL. Admittedly, confirmation that RANK protein is expressed by MSMs is lacking because of difficulties in detecting cellular RANK on murine primary cells. It would therefore be of interest to scrutinize the medullary zone during an ongoing immune reaction to find out whether MSMs can acquire features of SSMs in an environment rich in other RANKL-producing cells such as activated T cells and type 3 innate lymphoid cells (Bando et al., 2018; Josien et al., 1999).

We have previously shown that LECs respond to RANKL by the expression of ITGA2b (Cordeiro et al., 2016) and here we confirmed this sensitivity to RANKL using MAdCAM-1 (Cohen et al., 2014; Cordeiro et al., 2016). The absence of MAdCAM-1 expression by LECs lacking RANK had no impact on the presence of MAdCAM-1 on MRCs. This indicates that its presence on MRCs is not secondary to cell-membrane sharing with LECs and invokes post-transcriptional mechanisms to explain the increased MAdCAM-1 expression by MRCs compared to TRCs (Rodda et al., 2018). Deleting RANK from LECs had a clear impact on both SM subtypes when gene excision occurred during late embryogenesis and the first postnatal weeks. This is compatible with a critical role of RANK-activation of LECs when SMs start

occupying the embryonic LN anlagen and throughout the LN growth phase of the first few weeks. Once the SM population was established and maximal LN organ size had been attained, the importance of RANK for the LECs was minimal. Although RANK activation of LECs was required for the accumulation of embryonic macrophages in the LN anlagen, evidence is so far lacking to propose a direct relationship between the control over macrophage arrival and the future presence of SMs in the adult. Further studies are necessary to understand the molecular and cellular processes that oversee the formation of the complete macrophage compartment in the developing LN. Of further complication is the presence of the basement membrane of subcapsular and medullary sinuses (Pfeiffer et al., 2008), an extracellular matrix that not only serves as cell-anchoring substrate but may also affect cell differentiation. We cannot formally rule out a function of RANK-activated LECs in the maintenance of the SM compartment, but, because of the slow SM replacement rate, at least in the adult, it is likely that the consequences of Rank-deletion in LECs will only be noticeable months later. Of note, reconstitution of the SM population requires months after clodronated lipososome-mediated ablation (Delemarre et al., 1990). Yet, when the SM compartment was "emptied" by inflammation, RANK activation of LECs was clearly mandatory to fully reconstitute the SM pool. The finding that SSMs and MSMs were slowly replaced from CD45.1⁺ bone marrow precursors in the shielded irradiation experiments supports the idea of an input from an external (circulating) source under situations of inflammation. As a consequence of incomplete macrophage replenishment, subsequent immune reactions against the MVA virus were significantly diminished. Under these inflammatory conditions, it would be again of interest to determine whether activated T cells and type 3 innate lymphoid cells provide RANKL in addition to MRCs.

The analysis of the gene profiles provided information on the downstream pathways and the effector molecules produced by LECs. Loss of *Ccl20* expression and upregulation of *Ackr4/Ccrl1* in RANK-deficient LECs suggest a role in chemotaxis. Increased CCL20 production has also been observed in astrocytes in response to RANKL (Guerrini et al., 2015). In the LN, this chemokine plays a role in the recruitment of CCR6⁺ innate-like lymphocytes to the subcapsular area (Zhang et al., 2016). ACKR4/CCRL1 is produced by the subscapular ceiling layer of LECs but not by the floor layer (Ulvmar et al., 2014). Mice lacking the CCL20 receptor CCR6 comprise a normal SM compartment (Zhang et al., 2016), but whether ACKR4/CCRL1 affects the SMs has not been reported. Expression of MAdCAM-1 and ITGA2b was validated on the mRNA and the protein level. Intriguingly, the neutralization of MAdCAM-1 in developing LNs leads to more LN macrophages while lymphocyte numbers are reduced (Mebius et al., 1996). However, the interpretation of this result is complicated by the fact that MAdCAM-1 is also expressed by BECs and plays an important role in the recruitment of lymphocytes. ITGA2b is not expressed by LN BECs, and, although this integrin is already expressed by LECs of the LN anlagen (Bovay et al., 2018; Cordeiro et al., 2016), a defect in the SM compartment is not observed in *Itga2b*^{-/-} mice (Cordeiro et al., 2016). Taken together, the data suggest that LECs affect the recruitment and/or retention of SMs or their progenitors, but a direct impact on cell differentiation is not excluded.

Clinical use of RANKL-antagonists is approved to treat osteoporosis and bonemetastasizing cancers such as mammary and prostate carcinoma (Ahern et al., 2018). In the light of our findings, the impact of RANKL-neutralization on immune responses should be carefully evaluated. Notably, it has been shown that SSMs can function as tumor suppressor cells (Pucci et al., 2016). In accord with the concept that peripheral tissues, including lymphoid organs, shape resident immune cell composition, we demonstrated here that mesenchymal cells and LECs are essential elements to shape the niche for sinusoidal LN macrophages. Our findings are likely of importance to further advance current immunotherapies.

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Author contributions

AC, OGC, FA, JS, MC, LO, KA performed and analyzed experiments, MT, BL, HY provided reagents, and VF, AC and CGM designed the experiments and wrote the manuscript.

Declaration of interests

The authors declare no competing interest.

Main figure titles and legends

Figure 1. RANKL specifically expressed in LTOs and MRCs is deleted in *Ccl19-cre Rankl*^{*fl/fl*} mice. (A) E17.5 inguinal LNs of *Ccl19-cre Rankl*^{*fl/fl*} (*Rankl*^{*ACcl19*}) mice and *Rankl*^{*fl/fl*} control littermates were stained for LECs (mCLCA1), LTi cells (CD4) and RANKL. Scale bars represent 50 μ m. (B) Popliteal LNs of adult *Rankl*^{*ACcl19*} mice and control littermates were stained for B220 and RANKL. Scale bars represent 200 μ m. (C) Flow cytometry gating strategy to identify MRCs among the LN stromal cells. (D) The proportion of MRCs (MAdCAM-1⁺ VCAM-1⁺ cells) was determined in *Rankl*^{*ACcl19*} and *Rankl*^{*fl/fl*} control mice. (E) Relative *Rankl* mRNA expression in MRCs and the remaining (r.) stroma of *Rankl*^{*ACcl19*} and control mice. ND= not detected. The data are the mean ± SEM with individual data points; each point represents the value of pooled peripheral LNs of one mouse. Statistical significance (Mann-Whitney): ***=p<0.001, ns=not significant.

See also Figure S1.

Figure 2. Stromal RANKL deficiency results in the loss of sinusoidal macrophages. (A) Adult popliteal LN sections from *Ccl19-cre Rankl*^{*fl/fl*} (*Rankl*^{*ACcl19*}) mice and *Rankl*^{*fl/fl*} control littermates were stained for CD169, SIGN-R1, CD11b and B220. Scale bars represent 200 μ m. (B) Flow cytometry gating strategy to identify subcapsular sinus macrophages (SSMs) and medullary sinus macrophages (MSMs) in the LNs of *Rankl*^{*ACcl19*} and *Rankl*^{*fl/fl*} mice. The graphs depict their absolute cell numbers. (C) Flow cytometry gating strategy to identify F4/80⁺ CD169⁻ and F4/80⁻ CD169⁻ macrophages (MS) in the LNs of *Rankl*^{*ACcl19*} and *Rankl*^{*fl/fl*} mice. The graphs depict their absolute cell numbers. (D) Gating strategy to identify LN-resident and tissue-derived dendritic cells (DC) in the LNs of *Rankl*^{*ACcl19*} and *Rankl*^{*fl/fl*} mice. Their absolute numbers are shown. The data are the mean ± SEM with individual data points from inguinal, brachial and auricular LNs. Statistical significance (Mann-Whitney): ****=p<0.0001, *=p<0.05, ns=not significant.

Figure 3. Stromal RANKL deficiency leads to defects in immunity. (A) Gating strategy to identify the B cells of popliteal LNs that had captured PE-immune complexes delivered by intra-foot pad (i.fp.) injection of PE following passive immunisation with anti-PE antibody. To assure that B cells were not labelled during the cell manipulation, lymphocytes from CD45.1 (Ly5.1) mice were added to the cell suspension. The graph shows the proportion of B cells having captured PE in *Rankl^{ΔCc/19}* and *Rankl^{fl/fl}* mice. (B) RANKL-mutant or control mice received an i.fp. injection of 10⁶ pfu of vesicular stomatitis virus (VSV), and 6h later popliteal LN sections were stained for CD169, SIGN-R1 and the anti-VSV-glycoprotein antibody Vi10. Scale bars

represent 200 μ m. The graph depicts the quantification of the VSV⁺ area normalized to LN size. The data are the mean ± SEM with individual data points. (C) Popliteal LN cellularity was determined in PBS-treated control mice and in *Rankl^{ACc/19}* and *Rankl^{fl/fl}* mice 7 days after i.fp. injection of 10⁴ pfu of Modified Vaccinia Ankara (MVA) virus. (D) Flow cytometry profiles of B220⁺ GL-7⁺ Fas⁺ germinal center B cells and B220⁺ CD138⁺ plasma cells in popliteal LNs from PBS-mock or MVA-infected mice. The proportion and the number of germinal center B cells and plasma cells are shown in the graphs. The data are the mean ± SEM with individual data points and are representative of three independent experiments. Statistical significance (Mann-Whitney): *=p<0.05, **p<0.005, ns=not significant.

Figure 4. RANKL directly activates the subcapsular sinus macrophages. (A) Adult brachial LN sections from *Rank*^{*fi/fi*} control and *Cd169-cre Rank*^{*fi/fi*} (*Rank*^{*ACd169*}) mice were stained for CD169, SIGN-R1 and CD11b. Scale bars represent 200 μ m. The insets show higher magnification of the area around a B cell follicle "B". Scale bar is 100 μ m. (B) The number of subcapsular sinus macrophages (SSMs) and medullary sinus macrophages (MSMs) were determined in *RankI*^{*ACd169*} and *Rank*^{*fi/fi*} mice. The data are shown as the mean ± SEM with individual data points of inguinal and brachial LNs. Statistical significance (Mann-Whitney): ***=p<0.001, ns=not significant. (C) Adult C57BL/6 mice received 20 μ g of anti-RANKL antibody IK22-5, LTbR-Fc or TNFR2-Fc 3 times a week for 3 weeks, and the number of SMs was assessed in inguinal and brachial LNs. Statistical significance (one-way ANOVA with Bonferroni correction): ****=p<0.0001, ns=not significant.

See also Figures S2 and S3.

Figure 5. RANK-signaling of lymphatic endothelial cells is required for both sinusoidal macrophage subsets. (A-D) RANK deficiency in lymphatic endothelial cells (LECs) was induced by tamoxifen delivery to *Prox1-cre*^{ERT2} *Rank*^{fl/fl} mice (*Rank*^{ΔProx1}) at different ages. As control, *Rank*^{fl/fl} mice were treated identically. Tamoxifen administration was started at 4 weeks (A), 2 weeks (B), at E18.5 (C) and at postnatal days 1 to 4 (D) and then every 2 weeks until analysis. (A-C) Popliteal LN sections were stained for mCLCA1 (LECs), MAdCAM-1, SIGN-R1, CD169 and counterstained with DAPI. Scale bars represent 200 µm. (A, B, D) The numbers of subcapsular sinus macrophages (SSMs) and medullary sinus macrophages (MSMs) were determined in the LNs. The data are the mean \pm SEM with individual data points of inguinal and brachial LNs. Statistical significance (Mann-Whitney): **=p<0.01, ***=p<0.001, ns=not significant. See also Figure S4 and S5.

Figure 6. RANKL-activated lymphatic endothelial cells restore the sinusoidal macrophage compartment. (A) C57BL/6 mice received an intra footpad (i.fp.) injection of either PBS or CpG, and 4 days or 4 weeks afterwards popliteal LNs were stained for CD169, SIGN-R1 and CD11b. Scale bars represent 200 µm. (B,C) CpG was i.fp. administered to Prox1-cre^{ERT2} Rank^{fl/fl} mice $(Rank^{\Delta Prox1})$ and control $Rank^{fl/fl}$ mice, which then received tamoxifen as schematized. Five weeks afterwards, the popliteal LNs were (B) stained for CD169, SIGN-R1 and CD11b or (C) processed to assess the number of subcapsular sinus macrophages (SSMs) and medullary sinus macrophages (MSMs). Scale bars represent 200 µm. The graphs also show the number of SSMs and MSMs 4 days post i.fp. injection of CpG in C57BL/6 mice. The data are the mean \pm SEM with individual data points. (D) CpG was i.fp. administered to $Rank^{\Delta Prox1}$ and $Rank^{fl/fl}$ mice, which then received tamoxifen as depicted, and after 5 weeks the mice were immunized by an i.fp. injection of 10^4 pfu of Modified Vaccinia Ankara (MVA) virus. Seven days later the proportions and numbers of B220⁺ GL-7⁺ Fas⁺ germinal center B cells or B220⁺ CD138⁺ plasma cells in the popliteal LNs were determined. The data shown the mean \pm SEM with individual data points and are representative of three independent experiments. Statistical significance (Mann-Whitney): *=p<0.05, **=p<0.01.

Figure 7. RANK-activated LECs positive regulate the presence of CD11b⁺ myeloid cells. (A) Volcano Plot showing the genes whose expression is significantly reduced (blue) or increased (red) in LECs sorted from *Ccl19-cre Rankl*^{fl/fl} and *Rankl*^{fl/fl} control mice. Selected differentially expressed genes were indicated on the plot. (B) Selected genes that displayed changes in expression were validated by RT-qPCR on LECs sorted from *Prox1-cre Rank*^{fl/fl} mice versus control *Rank*^{fl/fl} mice. (C,D) *Prox1-cre*^{ERT2} *Rank*^{fl/fl} mice (*Rank*^{ΔProx1}) and control *Rank*^{fl/fl} mice versus control *Rank*^{fl/fl} mice. (C,D) *Prox1-cre*^{ERT2} *Rank*^{fl/fl} mice (*Rank*^{ΔProx1}) and control *Rank*^{fl/fl} mice received first an i.fp. administration of CpG, followed 5 days later by tamoxifen gavage. After 5 weeks, popliteal LNs were imaged for CD11b expression (C) that was (D) quantified as CD11b⁺ area normalized to LN area. (E) The number of CD11b^{Hi} cells were determined in the popliteal LNs by flow cytometry using the gating strategy described in Figure 2. The data are the mean ± SEM with individual data points of popliteal LNs. Statistical significance (Mann-Whitney): *=p<0.05. (F) Pregnant dams received tamoxifen at embryonic age E11.5 and E12.5 to trigger genetic *Rank* removal in LECs of embryos. Inguinal LN anlagen of *Rank*^{ΔProx1} and control *Rank*^{fl/fl} E17.5 embryos were stained for smooth muscle actin (SMA), LYVE-1 and CD11b in whole mounts. Scale bar represents 80 µm. (G) The number of CD11b⁺ cells was determined by

isosurface cell quantification in whole mount LN anlagen. The data show the mean \pm SD with individual data points. Statistical significance (Student's t-test): *=p<0.05. See also Figure S6

STAR Methods

CONTACT FOR REQUESTS AND RESOURCE SHARING

Further information and requests for resources and reagents should be directed to and will be fulfilled by the Lead Contact, Christopher Mueller (c.mueller@ibmc-cnrs.unistra.fr).

EXPERIMENTAL MODEL AND SUBJECT DETAILS

Mice

C57BL/6J (Charles River Laboratories, France), Ccl19-cre (Chai et al., 2013), Cd169-cre (Karasawa et al., 2015), *Prox1-cre^{ERT2}* (Bazigou et al., 2011), *Rankl^{fl/fl}* (Xiong et al., 2011), *Rank^{fl/fl}* (Rios et al., 2016), CAG-tdTomato and CD45.1 (Jackson Laboratories) mice were kept in specific pathogen-free conditions. Virus infections were carried out in A3 confined conditions with individual, filtered cages. Female and male mice were analyzed at adult age (7-10 weeks), unless specified, and age-matched littermates were used as controls. All transgenic or knock-in Cre mice as well as the dtTomato reporter mouse were used in heterozygous state. Tamoxifen (1 mg) was delivered to pregnant females by oral gavage at E11.5, E12.5 and at E18.5. Newborns were treated by intra-gastric injection of 50 μ g at P1 and 100 μ g from P2 to P4 (Pitulescu et al., 2010). Two-week old mice were gavaged with 0.5 mg tamoxifen/day on the first 2 days, and then a single 1 mg tamoxifen dose was delivered by gavage every 2 weeks. Adults (4 weeks onwards) were gavaged with 1 mg/day on the first 2 days and then a single 1 mg tamoxifen dose every 2 weeks. All experiments were carried out in conformity to the animal bioethics legislation approved by and according to national guidelines of the CREMEAS (Comité Régional d'Ethique en Matière d'Expérimentation Animale de Strasbourg) and the RCAI and Tokyo University of Pharmacy and Life Sciences animal use committee.

METHOD DETAILS

Immunizations and reagent administration

Passive immunization with PE-immune complexes and PE uptake were performed as described (Phan et al., 2009). In brief, mice were injected i.p. with 2 mg rabbit IgG anti-PE (Rocklands) 12-16 h before i.fp. administration of 10 μ g PE (Thermo Fisher). Mice were sacrificed 8 h later. For VSV infection, mice received an i.fp. injection of 10⁶ pfu of VSV (serotype Indiana, kind gift from S. Pfeffer, CNRS, Strasbourg), and 6h later the popliteal LNs were taken and imaged for VSV replication using the anti-VSV-glycoprotein antibody Vi10 (Honke et al., 2011). Mice received an i.fp. administration of 10⁴ pfu of MVA virus (kindly provided by Transgene, Illkirch, France), and 7 days later the popliteal LNs were taken. Mice were injected i.fp. with 10 μ g of CpG (ODN 2395, InvivoGen). To inhibit RANK, LTbR and TNFR signaling, adult C57BL/6 mice

received i.p. injections of 20 μ g of IK22-5, LTbR fused to murine IgG1 Fc or TNFR2-Fc (Etanercept) 3 times a week for 3 weeks.

Partial irradiation and adoptive transfer

Mice were anesthetized with a solution of ketamine and medetomidine and a 7 mm lead bridge placed over the upper back and head to shield the brachial LNs. The mice were then irradiated at a dose of 9.5 Gy from an X-ray source and reconstituted with 10⁷ bone marrow cells of Ly5.1/CD45.1 mice. After 4 weeks the blood chimerism and brachial LNs were analyzed.

Immunofluorescence of adult LN

LNs were freshly harvested from mice and embedded in OCT embedding matrix (Cell Path), or for tdTomato analysis pre-fixed in 4% PFA/PBS, and frozen in liquid nitrogen. Organs were cut into sections using the cryostat (Leica CM3050 S) and fixed in cold acetone for 20 min before freezing at -80°C. Sections were blocked with PBS containing 2% normal goat serum or 2% fetal bovine serum. For cell staining, antibodies and reagents were used (see key resource table) and DAPI (Sigma-Aldrich) was used to stain nuclei. Sections were mounted with Fluoromount-G (Invitrogen, Thermo Fisher Scientific). Images were acquired on a Microscope Zeiss Axio Observer Z1 Confocal LSM780 and LSM710 (Carl Zeiss) with the Carl Zeiss proprietary software Zen and on a spinning disk inverted microscope (Carl Zeiss) with a confocal head Yokogawa CSU and a Metamorph software (Metamorph). For *Cd169*-directed tdTomato expression analysis, sections were imaged using a Keyence BZ-X700 microscope. Analysis of all microscopic images was done using the open source imageJ-based Fiji distribution.

Immunofluorescence of embryonic LN anlagen

For histological analysis, embryos were fixed in 4% paraformaldehyde, dorsal and abdominal skin was removed together with the fat pad and directly used for immunofluorescence staining or for cryo-sectioning. Inguinal LN anlagen were identified by the bifurcation of major blood vessels in the inguinal fat pad. Whole mount or sections of LN anlagen were stained with mouse anti-mouse alpha smooth muscle actin-Cy3 (Sigma Aldrich), rat anti-mouse CD11b-A488 (Invitrogen, Thermo Fisher Scientific), rat anti-mouse CD169-A488, rat anti-mouse CD4-Pacific Blue and rat anti-mouse LYVE-1-A660 (Invitrogen, Thermo Fisher Scientific). Histomorphometric analysis, such as isosurface rendering and quantification of microscopic images was done using the open source imageJ-based Fiji software and Imaris, version 9 (Bitplane).

Isolation and analysis of LN cells

For stromal cells and macrophages, the LNs, cut into small pieces, were digested with an enzyme mix prepared in RPMI 1640 Gibco[®], 2% fetal bovine serum, and 1 mg/ml collagenase D

(Roche), 0.1 mg/ml DNase I (Roche), and 1 mg/ml Dispase II (Roche) at 37°C for 1 hour under agitation. Cells were gently homogenized by pipetting and the digestion stopped with EDTA. The cell suspension was filtered through a 100 μ m cell strainer. For stromal cell analysis and sorting, skin-draining LNs (inguinal, axillary, brachial, cervical, auricular, and popliteal) were pooled. Red blood cells were lysed in ammonium-chloride-potassium buffer (NH₄CL 0.15 M, KHCO₃ 1 mM, and EDTA 0.1 mM) for 1 min and the cells were washed. CD45⁺ and Ter119⁺ cells were depleted using microbeads (MACS Miltenyi Biotech) and also out-gated into a dump channel. Lymphocytes were isolated by crushing the LNs in PBS with a glass pestle and mortar followed by filtering the cells through a 40 μ m cell strainer (Becton Dickinson Biosciences).

Flow cytometry and immunofluorescence

Flow cytometry was performed on a Gallios (Beckman-Coulter) and analyzed with FlowJo software (Treestar). Cell sorting was performed on an ARIA (Becton Dickinson Biosciences). Binding to Fc receptor was blocked with FcR Blocking Reagent (Miltenyi Biotec) and 5% rat serum. DAPI or 7-AAD was used for exclusion of dead cells. Stromal cells were identified as live CD45⁻Ter119⁻gp38⁺ cells and MRCs as VCAM-1⁺ MAdCAM-1⁺ among them. For macrophages, following antibodies were used: CD11b (M1/70), CD11c (HL3), I-A/I-E (M5/114.15.2), CD169 (3D6-112), F4/80 (BM8) and CD45.1 (A20). Lymphocytes were stained for CD45R/B220 (RA3-6B2), CD3e (145-2C11), GL7 (GL7), CD95 (JO2), CD138 (281.2).

PCR

RNA was extracted using the RNeasy Mini or Micro kit (Qiagen) or NuceloSpin RNA Plus XS kit (Macherey-Nagel), and cDNA was synthesized with Maxima First Strand cDNA Synthesis Kit (Thermo Scientific) or Improm-II (Promega) using oligo(dT)15 primers. RT-PCR was performed using Luminaris color HiGreen qPCR Master Mix (Thermo Scientific). Quantitative RT-PCR was run on a Bio-Rad CFX96 thermal cycler, and threshold values (Ct) of the target genes "X" were normalized to housekeeping gene *β-actin* or *Gapdh* using the formula Δ Ct = Ct_x − Ct_{HKG}. The relative quantification was expressed as 2^{-ΔCt}. Genomic DNA was recovered from gDNA Removal Column XS of NuceloSpin RNA Plus XS kit (Macherey-Nagel) by washing with ethanol (70%) and elution with a small volume of DNAase-free water. PCR with the specific primers (see key resource table) was run on a Bio-Rad Thermal cycler C1000TM. PCR products were separated in agarose containing fluorescent nucleic acid dye (GelRed, Biotum). Photographic images were taken using U:Genius 3 (Syngene, Ozyme).

RNA sequencing and data processing

LEC mRNA profiles of 8 week old littermate (*Rankl*^{fl/fl}) and conditional RANKL-deficient (*Ccl19-cre Rankl*^{fl/fl}) mice were generated by deep sequencing. LECs were sorted from LNs by flow

cytometry on the basis of CD45⁻ TER119⁻ CD31⁺ podoplanin/gp38⁺ cells and RNA was harvested using Qiagen RNA isolation kit. cDNA was generated using the Takara SMART-Seqv4 Ultra Low Input RNA Kit and the library sequenced on Illumina Hiseq 4000 sequencer following Illumina's instructions. Quantification of gene expression was performed HTSeq v0.6.1 (Anders et al., 2015) using gene annotations from Ensembl release 81. Read counts were normalized across libraries (Anders et al., 2015), and low-abundance genes -on the basis of the mean reads \leq 1000- and highly variable genes SD \geq 1 were removed. Comparisons of interest were performed using the method previously described (Love et al., 2014). Resulting p-values were adjusted for multiple testing using the Benjamini and Hochberg method (Benjamini and Hochberg, 1995). Analysis was restricted to genes showing a P value < 0.05 and a 1.5 fold change difference between LECs sorted from *Ccl19-cre Rankl*^{fl/fl} and control mice. Plots have been generated using RStudio interface (ggplot2 package). Pathway analysis was performed using Metascape tool (http://metascape.org) on genes with reduced expression in *Ccl19-cre Rankl*^{fl/fl} mice than control. For each selected pathway, the top 30 genes were displayed with their associated Log2 fold change value.

QUANTIFICATION AND STATISTICAL ANALYSIS

Statistical analyses, as described in figure legends, were performed with Prism 5.0 (Graphpad Software Inc.). Data were analyzed with the Mann Whitney test, the non-paired Student's t-test or one-way ANOVA (with Bonferroni correction). A p-value of < 0.05 was considered as significant, *p < 0.05, **p < 0.01, ***p < 0.001, ***p<0.0001.

DATA AND SOFTWARE AVAILABILITY

The RNA-sequencing data has been deposited in the Gene Expression Omnibus public database under accession number GSE129315.

Excel table title and legends

Excel table 1. Relates to Figure 7. The table lists the genes whose expression is reduced in lymph node lymphatic endothelial cells of mice deficient in stromal RANKL.

Excel table 2. Relates to Figure 7. The table lists the genes whose expression increases in lymph node lymphatic endothelial cells of mice deficient in stromal RANKL.

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MHC-II

응 CD169

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CD11b

CD11c

































Rank ⊿Prox1

gene name ENSMUSG00000020953 ENSMUSG00000079022 ENSMUSG00000026639 ENSMUSG00000073643 ENSMUSG00000030516 ENSMUSG00000029373	Coch Col 22a 1 Lamb3 Wdfy1 Tjp 1 Pf4	raw P values Ad 2.90E-21 5.07E-56 4.95E-21 1.37E-28 8.58E-12 7.90E-08	ijusted P val Log 3.60E-18 6.93E-52 5.21E-18 6.26E-25 1.81E-09 5.20E-06	g fold change -4.844 -2.991 -2.821 -2.555 -2.136 -2.124
ENSMUSG00000017737	Mmp9	2.53E-10	3.11E-08	-1.743
ENSMUSG00000026712	Mrc1	1.56E-20	1.52E-17	-1.722
ENSMUSG0000002565	Scin	1.77E-08	1.39E-06	-1.720
ENSMUSG00000022479	Vdr	1.68E-10	2.30E-08	-1.714
ENSMUSG00000026874	Hc	5.92E-15	2.61E-12	-1.693
ENSMUSG0000027820	Mme	6.26E-12	1.40E-09	-1.669
ENSMUSG00000074491 ENSMUSG00000020701 ENSMUSG00000026390 ENSMUSG00000028100 ENSMUSG00000074207 ENSMUSG00000026121 ENSMUSG00000002020	Tmem132e Marco Nudt17 Adh1 Sema4c Ltbp2	1.57E-09 2.28E-21 9.19E-12 4.21E-03 1.89E-05 1.36E-07 2.08E-16	1.53E-07 3.12E-18 1.88E-09 3.38E-02 4.82E-04 8.10E-06 1.14E-13	-1.619 -1.503 -1.502 -1.484 -1.460 -1.451 -1.438
ENSMUSG0000060961 ENSMUSG00000029675 ENSMUSG0000009356 ENSMUSG00000030159 ENSMUSG00000055214 ENSMUSG00000040829	SIc4a4 Eln Lpo Clec1b Pld5 Zmynd15	2.05E-10 2.05E-11 1.56E-17 1.10E-02 3.01E-09 1.21E-05 2.05E-12	3.75E-09 1.12E-14 6.72E-02 2.80E-07 3.40E-04 5.18E-10	-1.436 -1.420 -1.384 -1.363 -1.354 -1.349
ENSMUSG0000031548	Sfrp1	7.93E-12	1.72E-09	-1.341
ENSMUSG00000071714	Csf2rb2	1.87E-11	3.46E-09	-1.297
ENSMUSG00000020592	Sdc1	1.17E-11	2.25E-09	-1.287
ENSMUSG00000026166	Ccl20	7.03E-08	4.73E-06	-1.275
ENSMUSG00000027358	Bmp2	2.75E-06	1.02E-04	-1.274
ENSMUSG00000030795	Fus	2.48E-02	1.19E-01	-1.263
ENSMUSG0000038608	Dock10	2.65E-11	4.47E-09	-1.254
ENSMUSG0000021732	Fgf10	1.12E-04	2.06E-03	-1.253
ENSMUSG00000040084	Bub1b	6.59E-13	1.80E-10	-1.246
ENSMUSG00000020661	Dnmt3a	7.07E-19	6.29E-16	-1.238
ENSMUSG00000033257	Ttll4	7.15E-12	1.58E-09	-1.238
ENSMUSG00000021573	Tppp	1.57E-09	1.53E-07	-1.230
ENSMUSG00000020042	Btbd11	8.86E-14	2.82E-11	-1.224
ENSMUSG00000024164	C3	8.19E-10	9.18E-08	-1.207
ENSMUSG00000001986	Gria3	2.39E-11	4.18E-09	-1.197
ENSMUSG00000022883	Robo1	2.55E-10	3.11E-08	-1.179
ENSMUSG00000091650	Apol11a	2.64E-07	1.47E-05	-1.178
ENSMUSG00000020593	Lpin1	9.20E-15	3.70E-12	-1.159
ENSMUSG00000026944	Abca2	2.40E-13	6.85E-11	-1.158
ENSMUSG0000027716	Trpc3	5.47E-08	3.72E-06	-1.137
ENSMUSG00000026587	Astn1	1.92E-08	1.47E-06	-1.129
ENSMUSG00000038894	Irs2	7.30E-10	8.25E-08	-1.129
ENSMUSG0000067764	XIr5c	1.96E-05	4.95E-04	-1.126
ENSMUSG00000042284	Itga1	2.25E-11	4.00E-09	-1.111
ENSMUSG00000022440	C1qtnf6	4.11E-06	1.41E-04	-1.111
ENSMUSG0000024899 ENSMUSG0000031266 ENSMUSG0000039621 ENSMUSG00000033149 ENSMUSG0000001864 ENSMUSG00000070000	Papss2 Gla Prex1 Phldb2 Aif1l Fcho1 Plokbg1	7.19E-08 3.42E-08 5.41E-14 3.33E-12 8.30E-06 1.13E-04 8.20E 15	4.82E-06 2.44E-06 1.80E-11 8.00E-10 2.48E-04 2.07E-03 2.44E 12	-1.104 -1.095 -1.083 -1.082 -1.073 -1.072 1.063
ENSMUSG00000026872	Zeb2	8.86E-09	7.52E-07	-1.055
ENSMUSG00000050199	Lgr4	5.47E-07	2.64E-05	-1.055
ENSMUSG00000036907	C1ql2	3.98E-06	1.37E-04	-1.054
ENSMUSG00000032735	Ablim3	2.49E-11	4.25E-09	-1.052
ENSMUSG00000060429	Sntb1	5.56E-06	1.81E-04	-1.050
ENSMUSG0000008318	Relt	6.50E-05	1.33E-03	-1.047
ENSMUSG0000018428	Akap1	2.81E-12	6.99E-10	-1.043
ENSMUSG0000006522	Itih3	3.14E-02	1.41E-01	-1.043
ENSMUSG00000039395	Mreg	3.97E-05	8.98E-04	-1.040
ENSMUSG00000070407	Hs3st3b1	1.20E-08	9.94E-07	-1.036
ENSMUSG00000026768	Itga8	3.90E-02	1.62E-01	-1.035
ENSMUSG00000027695	Pld1	2.93E-08	2.13E-06	-1.032
ENSMUSG00000074141 ENSMUSG00000015243 ENSMUSG00000075010 ENSMUSG00000031196 ENSMUSG00000055805 ENSMUSG00000028763 ENSMUSG00000001870	Abca 1 AW112010 F8 Fmnl 1 Hspg2 Ltbp1	1.75E-06 1.77E-08 2.99E-03 1.31E-09 9.58E-09 1.41E-05 1.44E-16	6.97E-03 1.39E-06 2.61E-02 1.35E-07 8.04E-07 3.88E-04 8.58E-14	-1.029 -1.026 -1.006 -1.006 -1.005 -0.991 -0.984
ENSMUSG0000030745	II 21r	1.09E-03	1.22E-02	-0.980
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ENSMUSG00000015957	Wnt11	1.45E-05	3.94E-04	-0.971
ENSMUSG00000032289	Thsd4	1.31E-10	1.87E-08	-0.958
ENSMUSG00000025332	Kdm5c	3.67E-15	1.67E-12	-0.956
ENSMUSG0000020310	Madcam1	2.88E-07	1.60E-05	-0.952
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ENSMUSG0000021338	Lrrc16a	1.72E-06	6.92E-05	-0.915
ENSMUSG00000044393	Dsg2	3.67E-09	3.39E-07	-0.912
ENSMUSG00000036144	Meox2	1.92E-08	1.47E-06	-0.912
ENSMUSG00000041992	Rapgef5	9.93E-08	6.20E-06	-0.909
ENSMUSG00000037885	Stk35	1.17E-13	3.63E-11	-0.904
ENSMUSG00000027276	Jag1	1.12E-11	2.18E-09	-0.904
ENSMUSG0000039304 ENSMUSG00000039835 ENSMUSG00000041720 ENSMUSG00000032115 ENSMUSG00000020422 ENSMUSG00000035493 ENSMUSG00000025153	Tnfsf10 Nhsl1 Pi4ka Hyou1 Tns3 Tgfbi Fasn	4.23E-07 1.00E-12 3.87E-10 1.27E-04 8.61E-08 6.37E-05 6 34E-09	2.17E-05 2.69E-10 4.52E-08 2.27E-03 5.58E-06 1.31E-03 5.52E-07	-0.901 -0.900 -0.898 -0.897 -0.889 -0.889 -0.889 -0.888
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ENSMUSG0000035078	Mtmr9	1.41E-05	3.88E-04	-0.870
ENSMUSG0000005672	Kit	5.36E-07	2.60E-05	-0.869
ENSMUSG00000036298	Slc2a13	2.63E-06	9.83E-05	-0.869
ENSMUSG00000032902	Slc16a1	9.41E-05	1.79E-03	-0.869
ENSMUSG00000033763	Mtss1l	2.61E-06	9.81E-05	-0.864
ENSMUSG00000027318	Adam33	1.94E-04	3.20E-03	-0.856
ENSMUSG00000024087	Cyp101	8.87E-06	2.62E-04	-0.856
ENSMUSG00000030737	Slco2b1	2.32E-06	8.91E-05	-0.856
ENSMUSG00000039005	Tlr4	6.14E-06	1.94E-04	-0.855
ENSMUSG00000029370	Rassf6	1.79E-03	1.79E-02	-0.855
ENSMUSG00000039456	Morc3	5.20E-07	2.55E-05	-0.840
ENSMUSG00000023088	Abcc1	1.67E-09	1.60E-07	-0.835
ENSMUSG00000061589	Dot11	1.20E-07	7.19E-06	-0.831
ENSMUSG0000027878	Notch2	2.12E-09	2.02E-07	-0.828
ENSMUSG00000033308	Dpyd	1.51E-05	4.07E-04	-0.828
ENSMUSG00000033943	Mga	1.76E-04	2.96E-03	-0.825
ENSMUSG00000032812	Arap1	9.44E-11	1.43E-08	-0.824
ENSMUSG0000004668	Abca13	2.20E-04	3.54E-03	-0.824
ENSMUSG00000021906	Oxnad1	1.06E-02	6.51E-02	-0.824
ENSMUSG0000026748	Plxdc2	1.83E-06	7.23E-05	-0.812
ENSMUSG00000034394	Lif	1.16E-06	4.93E-05	-0.811
ENSMUSG00000039298	Cdk5rap2	4.38E-07	2.23E-05	-0.811
ENSMUSG00000057596	Trim30d	3.05E-05	7.15E-04	-0.806
ENSMUSG00000020120	Plek	3.78E-04	5.42E-03	-0.806
ENSMUSG00000021703	Serinc5	6.01E-07	2.82E-05	-0.805
ENSMUSG00000022586	Ly6i	3.79E-04	5.43E-03	-0.804
ENSMUSG00000022380 ENSMUSG00000008193 ENSMUSG00000070939 ENSMUSG00000031441 ENSMUSG00000027698 ENSMUSG00000025612 ENSMUSG00000004266	Spib Tgfbrap1 Atp11a Nceh1 Bach1 Ptpn6	4.46E-04 1.20E-04 3.47E-07 4.56E-08 6.99E-07 3.15E-03	6.15E-03 2.17E-03 1.85E-05 3.20E-06 3.21E-05 2.71E-02	-0.803 -0.803 -0.802 -0.800 -0.799 -0.792
ENSMUSG0000024065 ENSMUSG0000096606 ENSMUSG00000023830 ENSMUSG00000038886 ENSMUSG00000035459 ENSMUSG00000079487	Ehd3 Gm4980 Igf2r Man2a2 Stab2 Med12 Chet7	2.13E-03 7.21E-05 1.23E-05 3.77E-06 1.70E-11 2.16E-04 7.87E-06	2.04E-02 1.44E-03 3.43E-04 1.32E-04 3.18E-09 3.50E-03	-0.788 -0.782 -0.781 -0.780 -0.779 -0.777
ENSMUSG00000037347 ENSMUSG00000026933 ENSMUSG00000032554 ENSMUSG00000015133 ENSMUSG00000052384 ENSMUSG00000020770 ENSMUSG00000021257	Camsap1 Trf Lrrk1 Nrros Unk Angel1	2.82E-06 2.82E-06 3.63E-05 3.99E-05 1.63E-03 1.17E-04 4.30E-03	2.38E-04 1.05E-04 8.29E-04 9.00E-04 1.67E-02 2.12E-03 3.43E-02	-0.773 -0.765 -0.758 -0.752 -0.748 -0.744 -0.743
ENSMUSG0000044674	Fzd1	1.15E-04	2.10E-03	-0.742
ENSMUSG00000047793	Sned1	2.03E-04	3.31E-03	-0.742
ENSMUSG00000010175	Prox1	3.60E-06	1.27E-04	-0.742
ENSMUSG00000079481	Nhs12	5.12E-04	6.80E-03	-0.740
ENSMUSG00000038371	Sbf2	1.21E-03	1.32E-02	-0.737
ENSMUSG0000038178	Slc43a2	1.10E-02	6.69E-02	-0.736
ENSMUSG0000020914	Top2a	6.69E-03	4.74E-02	-0.732
ENSMUSG00000057367	Birc2	8.73E-04	1.02E-02	-0.731
ENSMUSG00000032560	Dnajc13	3.03E-07	1.65E-05	-0.731
ENSMUSG00000025224	Gbf1	1.10E-04	2.05E-03	-0.730
ENSMUSG00000035941	Ibtk	4.69E-05	1.03E-03	-0.726
ENSMUSG00000026434	Nucks1	6.57E-05	1.34E-03	-0.725
ENSMUSG00000053080	2700081015Rik	2.74E-04	4.21E-03	-0.724
ENSMUSG0000007613	Tgfbr1	1.20E-06	5.07E-05	-0.724
ENSMUSG00000032000	Birc3	9.83E-06	2.82E-04	-0.722
ENSMUSG00000035200	Chrnb4	2.69E-03	2.42E-02	-0.720
ENSMUSG00000034220	Gpc1	5.65E-07	2.70E-05	-0.719
ENSMUSG00000022148	Fyb	3.36E-03	2.85E-02	-0.719
ENSMUSG00000037169	Mycn	1.20E-02	7.17E-02	-0.717
ENSMUSG0000032332	Col12a1	2.29E-07	1.30E-05	-0.714
ENSMUSG0000001128	Cfp	9.62E-03	6.11E-02	-0.710
ENSMUSG00000042350	Arel1	7.06E-05	1.42E-03	-0.704
ENSMUSG00000029287	Tgfbr3	7.28E-06	2.22E-04	-0.703
ENSMUSG00000062232	Rapgef2	3.87E-08	2.73E-06	-0.699
ENSMUSG00000033386	Frrs1	1.88E-05	4.79E-04	-0.698
ENSMUSG00000030930	Chst15	1 99E-04	3.26E-03	-0.696
ENSMUSG00000030930 ENSMUSG00000028556 ENSMUSG00000032086 ENSMUSG00000062960 ENSMUSG00000024665 ENSMUSG00000033792 ENSMUSG00000036529	Dock7 Bace1 Kdr Fads2 Atp7a Sbf1	5.40E-04 6.17E-06 9.53E-10 1.90E-03 7.70E-05 1.56E-03	5.26E-03 7.05E-03 1.94E-04 1.03E-07 1.88E-02 1.51E-03 1.62E-02	-0.696 -0.695 -0.695 -0.690 -0.689 -0.689 -0.688
ENSMUSG0000020300	Cpeb4	5.67E-07	2.70E-05	-0.687
ENSMUSG00000053641	Dennd4a	1.72E-03	1.73E-02	-0.687
ENSMUSG00000038521	C1s1	4.22E-05	9.41E-04	-0.687
ENSMUSG00000033278	Ptprm	4.18E-06	1.43E-04	-0.686
ENSMUSG0000000305	Cdh4	4.01E-03	3.25E-02	-0.685
ENSMUSG00000102329	Gm10851	6.53E-04	8.17E-03	-0.683
ENSMUSG00000031216	Stard8	2.71E-03	2.43E-02	-0.682
ENSMUSG00000051379	Flrt3	5.86E-06	1.87E-04	-0.681
ENSMUSG00000028339	Col15a1	3.59E-02	1.54E-01	-0.680
ENSMUSG00000020827	Mink1	1.20E-04	2.17E-03	-0.679
ENSMUSG00000039115	Itga9	2.77E-08	2.04E-06	-0.678
ENSMUSG00000079484	Phyhd1	4.30E-03	3.43E-02	-0.678
ENSMUSG00000029992	Gfpt1	3.19E-04	4.74E-03	-0.675
ENSMUSG0000034422	Parp14	6.80E-05	1.38E-03	-0.674
ENSMUSG0000026193	Fn1	1.05E-03	1.19E-02	-0.673
ENSMUSG00000032572	Col6a4	1.47E-02	8.29E-02	-0.673
ENSMUSG00000026335	Pam	1.37E-03	1.48E-02	-0.668
ENSMUSG00000023994	Nfya	3.95E-04	5.63E-03	-0.667
ENSMUSG00000051855	Mest	1.03E-04	1.93E-03	-0.667
ENSMUSG0000039286	Fndc3b	1.50E-04	2.62E-03	-0.667
ENSMUSG00000036792	Mbd5	2.70E-04	4.17E-03	-0.666
ENSMUSG00000067851	Arfgef1	2.23E-05	5.48E-04	-0.665
ENSMUSG00000026657	Frmd4a	2.42E-06	9.22E-05	-0.664
ENSMUSG00000074151	NIrc5	1.15E-05	3.24E-04	-0.664
ENSMUSG00000027962	Vcam1	5.07E-04	6.75E-03	-0.662
ENSMUSG00000035356	Nfkbiz	1.23E-02	7.28E-02	-0.662
ENSMUSG0000031434	Morc4	3.89E-06	1.36E-04	-0.659
ENSMUSG00000031129	Sl c9a 9	3.12E-04	4.67E-03	-0.657
ENSMUSG00000035273	Hpse	1.85E-03	1.84E-02	-0.656
ENSMUSG00000040690	Col 16a 1	9.55E-05	1.81E-03	-0.655
ENSMUSG00000070733	Fryl	2.97E-03	2.60E-02	-0.655
ENSMUSG00000074577	Fam65c	3.51E-04	5.13E-03	-0.652
ENSMUSG0000066232	Ipo7	1.49E-05	4.04E-04	-0.649
ENSMUSG00000018068	Ints2	5.95E-04	7.60E-03	-0.648
ENSMUSG00000033209	Ttc28	1.43E-06	5.91E-05	-0.648
ENSMUSG00000022371	Col14a1	3.29E-03	2.80E-02	-0.647
ENSMUSG00000022197	Pdzd2	4.08E-04	5.77E-03	-0.647
ENSMUSG00000054252	Fgfr3	3.20E-03	2.74E-02	-0.645
ENSMUSG00000032487	Ptgs2	3.57E-03	3.00E-02	-0.643
ENSMUSG0000071713	Csf2rb	2.49E-05	6.02E-04	-0.643
ENSMUSG00000024483	Ankhd1	5.87E-05	1.23E-03	-0.639
ENSMUSG00000031877	Ces2g	5.33E-05	1.14E-03	-0.639
ENSMUSG0000009376	Met	3.63E-04	5.27E-03	-0.638
ENSMUSG00000005397	Nid1	3.21E-05	7.46E-04	-0.636
ENSMUSG0000003226	Ranbp2	1.49E-06	6.13E-05	-0.636
ENSMUSG00000031886 ENSMUSG00000001376 ENSMUSG00000036833 ENSMUSG00000033902 ENSMUSG00000016918 ENSMUSG00000018209 ENSMUSG0000000631	Ccdc132 Pnpla7 Mapkbp1 Sulf1 Stk4 Myo18a	4.95E-06 1.11E-02 1.58E-03 3.71E-03 8.19E-04 4.49E-06	1.59E-02 1.65E-04 6.73E-02 1.64E-02 3.08E-02 9.72E-03 1.51E-04	-0.636 -0.634 -0.631 -0.631 -0.630 -0.629
ENSMUSG0000017493 ENSMUSG00000106847 ENSMUSG00000054555 ENSMUSG00000035248 ENSMUSG00000024042 ENSMUSG00000038518	Igfbp4 Peg13 Adam12 Zcchc6 Sik1 Jarid2	1.19E-02 1.06E-03 6.46E-03 1.12E-03 3.33E-04 5.17E-04 5.70E-04	7.13E-02 1.20E-02 4.62E-02 1.24E-02 4.89E-03 6.84E-03 7.23E.02	-0.629 -0.627 -0.627 -0.626 -0.626 -0.625
ENSMUSG00000034109 ENSMUSG00000073489 ENSMUSG00000098973 ENSMUSG00000009621 ENSMUSG00000034947 ENSMUSG00000030257 ENSMUSG00000028465	Gorrm4 Ifi 204 Mir6236 Vav2 Tmem106a Srgap3 Tln1	5.70E-04 9.74E-03 3.21E-02 6.15E-04 3.90E-03 2.34E-03 4.92E-05	7.33E-03 6.15E-02 1.43E-01 7.80E-03 3.19E-02 2.19E-02 1.07E-03	-0.624 -0.624 -0.623 -0.623 -0.621 -0.621
ENSMUSG0000010277	2610507B11Rik	1.55E-04	2.68E-03	-0.620
ENSMUSG0000005973	Rcn1	2.79E-04	4.26E-03	-0.618
ENSMUSG00000024754	Tmem2	1.23E-03	1.34E-02	-0.617
ENSMUSG00000029998	Pcyox1	4.14E-05	9.28E-04	-0.616
ENSMUSG00000029135	Fos12	5.07E-06	1.68E-04	-0.616
ENSMUSG00000070639	Lrrc8b	5.62E-06	1.82E-04	-0.615
ENSMUSG00000034709 ENSMUSG00000029385 ENSMUSG00000021670 ENSMUSG00000028991 ENSMUSG00000038058 ENSMUSG00000024610	Ppp1r21 Ccng2 Hmgcr Mtor Nod1 Cd74	9.61E-06 1.67E-04 3.52E-05 6.64E-03 1.92E-03 5.56E-04	2.78E-02 2.78E-04 2.84E-03 8.05E-04 4.71E-02 1.88E-02 7.20E-03	-0.611 -0.608 -0.606 -0.605 -0.605 -0.604
ENSMUSG0000013089	Etv5	1.75E-03	1.75E-02	-0.602
ENSMUSG0000027288	Zfp106	2.40E-04	3.79E-03	-0.601
ENSMUSG00000034664	Itga2b	4.51E-04	6.19E-03	-0.600
ENSMUSG00000038250	Usp38	7.35E-04	8.96E-03	-0.599
ENSMUSG00000032946	Rasgrp2	2.27E-04	3.61E-03	-0.599
ENSMUSG00000023991	Foxp4	2.36E-05	5.78E-04	-0.597
ENSMUSG00000022425	Enpp2	1.44E-03	1.52E-02	-0.597
ENSMUSG00000041685	Fcho2	2.74E-04	4.21E-03	-0.596
ENSMUSG00000031828	Klhl36	8.96E-06	2.65E-04	-0.596
ENSMUSG00000054008	Ndst1	6.18E-04	7.83E-03	-0.595
ENSMUSG00000018909	Arrb1	1.71E-05	4.46E-04	-0.595
ENSMUSG00000026640	Plxna2	1.71E-03	1.73E-02	-0.594
ENSMUSG00000051786	Tubgcp6	8.93E-03	5.82E-02	-0.593
ENSMUSG0000039831	Arhgap29	2.45E-05	5.94E-04	-0.593
ENSMUSG00000026179	Pnkd	1.13E-03	1.26E-02	-0.592
ENSMUSG00000019951	Uhrf1bp1l	1.64E-03	1.68E-02	-0.591
ENSMUSG00000027425	Csrp2bp	4.19E-02	1.69E-01	-0.590
ENSMUSG0000005871	Apc	4.35E-04	6.05E-03	-0.587
ENSMUSG00000054387	Mdm4	8.99E-04	1.05E-02	-0.587
ENSMUSG00000023118 ENSMUSG00000036990 ENSMUSG00000005087 ENSMUSG00000039607 ENSMUSG00000024378 ENSMUSG00000037791 ENSMUSG00000004085	Otud4 Cd44 Rbms3 Stard4 Phf12 Zak	2.88E-03 9.18E-03 2.80E-03 7.64E-03 2.93E-02 1.61E-04	1.75E-02 2.54E-02 5.92E-02 2.49E-02 5.20E-02 1.33E-01 2.75E-03	-0.585 -0.585 -0.581 -0.580 -0.580 -0.579 -0.579
ENSMUSG0000029119 ENSMUSG0000028842 ENSMUSG0000020303 ENSMUSG00000024399 ENSMUSG00000050812 ENSMUSG00000047045	Man2b2 Ago3 Stc2 Ltb AI314180 Tmem164 Typdc16	5.81E-06 1.63E-03 5.52E-03 7.75E-04 5.33E-03 1.48E-05	1.87E-04 1.68E-02 4.11E-02 9.32E-03 4.03E-02 4.01E-04 2.10E-02	-0.578 -0.577 -0.577 -0.574 -0.573 -0.572
ENSMUSG00000021830 ENSMUSG00000032193 ENSMUSG00000040850 ENSMUSG00000004626 ENSMUSG00000050967 ENSMUSG00000036339 ENSMUSG00000027177	LdIr Psme4 Stxbp2 Creg2 Tmem260 Hipk3	4.21E-04 7.73E-04 1.83E-04 3.76E-03 5.51E-03 7.19E-03	5.90E-03 9.31E-03 3.06E-03 3.10E-02 4.11E-02 4.99E-02	-0.571 -0.571 -0.569 -0.569 -0.569 -0.568
ENSMUSG0000042410	Agps	1.82E-05	4.68E-04	-0.563
ENSMUSG0000030787	Lyve1	9.30E-03	5.97E-02	-0.563
ENSMUSG00000033487	Fndc3a	7.29E-06	2.22E-04	-0.560
ENSMUSG00000039328	Rnf122	7.69E-03	5.23E-02	-0.560
ENSMUSG00000031209	Heph	6.18E-04	7.83E-03	-0.559
ENSMUSG00000041638	Gcn1l1	5.17E-04	6.85E-03	-0.557
ENSMUSG00000046862	Pramef8	7.08E-05	1.42E-03	-0.557
ENSMUSG0000023034 ENSMUSG00000044783 ENSMUSG00000029787 ENSMUSG00000025958 ENSMUSG00000066595 ENSMUSG0000000275	Nr4a 1 Hjurp Avl 9 Creb 1 Mfs d 7b Tri m 25	3.42E-02 1.22E-03 8.78E-03 1.22E-05 4.44E-04 7.54E-05	1.49E-03 1.49E-01 1.33E-02 5.75E-02 3.41E-04 6.12E-03 1.49E-03	-0.554 -0.554 -0.554 -0.553 -0.553 -0.552
ENSMUSG0000026674	Ddr2	1.27E-04	2.28E-03	-0.551
ENSMUSG00000030207	8430419L09Rik	1.72E-02	9.27E-02	-0.551
ENSMUSG00000020053	Igf1	9.50E-03	6.06E-02	-0.550
ENSMUSG00000026782	Abi2	2.28E-03	2.15E-02	-0.549
ENSMUSG00000022146	Osmr	2.90E-03	2.55E-02	-0.548
ENSMUSG00000064289	Tank	7.65E-03	5.21E-02	-0.547
ENSMUSG00000024085	Man2a1	1 86E-02	9 79E-02	-0.547
ENSMUSG0000029313	Aff1	1.25E-06	5.24E-05	-0.545
ENSMUSG00000040297	Suco	3.78E-05	8.58E-04	-0.544
ENSMUSG00000035314	Gdpd5	1.51E-06	6.19E-05	-0.543
ENSMUSG00000030946	Lhpp	4.24E-03	3.39E-02	-0.543
ENSMUSG00000026112	Coa5	1.12E-03	1.25E-02	-0.543
ENSMUSG00000020021	Fgd6	4.08E-03	3.29E-02	-0.543
ENSMUSG00000057133	Chd6	1.19E-03	1.31E-02	-0.539
ENSMUSG00000017548	Suz12	3.19E-04	4.74E-03	-0.538
ENSMUSG00000029101	Rgs12	5.73E-05	1.21E-03	-0.537
ENSMUSG00000002222	Rmnd5a	4.70E-04	6.40E-03	-0.537
ENSMUSG00000050912	Tmem123	2.27E-04	3.61E-03	-0.534
ENSMUSG00000026170	Cyp27a1	1.05E-02	6.48E-02	-0.533
ENSMUSG00000038545	Cul7	4.91E-04	6.66E-03	-0.532
ENSMUSG0000000823 ENSMUSG00000023206 ENSMUSG00000038564 ENSMUSG00000020101 ENSMUSG00000027351 ENSMUSG0000032740	Znf512b Il 15ra Ift172 4632428N05Rik Spred1 Ccdc88a Gng12	6.37E-03 9.42E-04 2.54E-04 2.04E-04 5.34E-04 3.39E-04	4.58E-02 1.09E-02 3.96E-03 3.33E-03 7.02E-03 4.98E-03	-0.532 -0.531 -0.531 -0.529 -0.529 -0.529
ENSMUSG0000029059 ENSMUSG00000038866 ENSMUSG00000041936 ENSMUSG00000036356 ENSMUSG0000069662 ENSMUSG00000027189	Fam213b Zcchc2 Agrn Csgalnact1 Marcks Trim44	9.14E-04 2.47E-02 9.16E-04 3.01E-03 3.26E-06 4.87E-03 1.11F-04	1.00E-02 1.19E-01 1.06E-02 2.62E-02 1.19E-04 3.75E-02 2.06E-03	-0.528 -0.527 -0.527 -0.525 -0.525 -0.525 -0.523
ENSMUSG0000018417	Myo1b	1.64E-05	4.33E-04	-0.523
ENSMUSG00000021340	Gpld1	1.15E-02	6.92E-02	-0.522
ENSMUSG00000015189	Casd1	8.87E-04	1.04E-02	-0.522
ENSMUSG00000028980	H6pd	1.15E-02	6.92E-02	-0.522
ENSMUSG00000029647	Pan3	9.12E-05	1.74E-03	-0.521
ENSMUSG00000040761	Spen	4.77E-03	3.69E-02	-0.520
ENSINUSG0000029407 ENSMUSG00000014599 ENSMUSG00000024294 ENSMUSG00000020841 ENSMUSG00000032220 ENSMUSG00000079037 ENSMUSG00000022827	Csf1 Mib1 Cpd Myo1e Prnp Iqcb1	1.44E-03 9.58E-04 7.91E-04 1.69E-03 8.46E-03 7.29E-03 2.19E-04	1.52E-02 1.10E-02 9.46E-03 1.72E-02 5.61E-02 5.04E-02 3.53F-02	-0.520 -0.519 -0.519 -0.519 -0.519 -0.519 -0.517
ENSMUSG0000020057	Dram1	2.42E-03	2.24E-02	-0.517
ENSMUSG00000029708	Gcc1	1.22E-02	7.24E-02	-0.516
ENSMUSG00000034210	Efcab14	2.53E-06	9.54E-05	-0.516
ENSMUSG00000025085	Ablim1	9.11E-03	5.89E-02	-0.515
ENSMUSG00000059981	Taok2	1.43E-04	2.53E-03	-0.515
ENSMUSG00000020486	Sept4	5.47E-04	7.13E-03	-0.515
ENSMUSG0000045312	LIITPI 2	2.13E-03	2.04E-02	-0.515
ENSMUSG00000024169	Ift140	1.63E-03	1.68E-02	-0.515
ENSMUSG00000042446	Zmym4	8.65E-03	5.69E-02	-0.514
ENSMUSG00000020077	Srgn	9.94E-03	6.25E-02	-0.514
ENSMUSG00000028960	Ube4b	2.21E-04	3.54E-03	-0.513
ENSMUSG00000024163	Mapk8ip3	1.21E-02	7.20E-02	-0.513
ENSMUSG00000022876	Smap2	5.76E.00	1.86F-04	-0.513
ENSMUSG0000076435	Acsf2	2.58E-02	1.22E-01	-0.512
ENSMUSG0000036352	Ubac1	1.30E-02	7.56E-02	-0.512
ENSMUSG00000037685	Atp8a1	1.32E-02	7.65E-02	-0.512
ENSMUSG00000031229	Atrx	5.82E-05	1.23E-03	-0.511
ENSMUSG00000034663	Bmp2k	1.80E-03	1.79E-02	-0.510
ENSMUSG0000029202	Pds5a	2.18E-03	2.08E-02	-0.510
ENSINUSG0000026491 ENSMUSG00000052593 ENSMUSG00000054874 ENSMUSG00000027750 ENSMUSG00000051329 ENSMUSG00000036330 ENSMUSG00000041202	Adam17 Pcnxl3 Postn Nup160 Slc18a1 Gtf3c3	9.26E-04 5.57E-04 2.53E-03 3.78E-02 5.82E-04 1.52E-02 1.83E-02	1.0/E-02 7.20E-03 2.31E-02 1.59E-01 7.45E-03 8.52E-02 9.70E-02	-0.509 -0.508 -0.505 -0.505 -0.504 -0.504 -0.504
ENSMUSG00000024393 ENSMUSG0000024393 ENSMUSG0000024393 ENSMUSG00000021806 ENSMUSG00000024522	Kif1b Ppp1r16a AU040320 Prrc2a Nid2 Chn2	2.27E-02 2.27E-03 1.12E-02 3.96E-06 1.14E-02 1.15E-03 1 59E 02	2.14E-02 6.80E-02 1.37E-04 6.88E-02 1.27E-02 1.65F-02	-0.504 -0.503 -0.503 -0.502 -0.500 -0.500

ENSMUSG00000025855Prkarib1.05E-144.10E-12ENSMUSG00000030865Chp25.25E-046.92E-03ENSMUSG0000060572Mfap22.17E-055.37E-04ENSMUSG00000047821Trim162.84E-151.39E-12ENSMUSG00000079355Ackr43.99E-072.07E-05ENSMUSG00000034981Parm11.96E-081.49E-06ENSMUSG00000020577Tspan132.20E-081.64E-06ENSMUSG00000020577Tspan132.35E-229.14E-19ENSMUSG00000032548Slco2a11.33E-081.09E-06ENSMUSG00000039405Prss231.41E-078.33E-06ENSMUSG00000044337Ackr38.18E-097.03E-07ENSMUSG00000025608Podxl9.00E-062.65E-04ENSMUSG00000051022Hs3st13.31E-032.81F-02	0.601
ENSMUSG00000047821Trim162.84E-151.39E-12ENSMUSG00000079355Ackr43.99E-072.07E-05ENSMUSG00000034981Parm11.96E-081.49E-06ENSMUSG00000020577Tspan132.20E-081.64E-06ENSMUSG0000004655Aqp15.35E-229.14E-19ENSMUSG00000032548Slco2a11.33E-081.09E-06ENSMUSG00000039405Prss231.41E-078.33E-06ENSMUSG00000044337Ackr38.18E-097.03E-07ENSMUSG00000025608Podxl9.00E-062.65E-04ENSMUSG00000051022Hs3st13.31E-032.81F-02	
ENSMUSG0000020577Tspan132.20E-081.64E-06ENSMUSG0000004655Aqp15.35E-229.14E-19ENSMUSG0000032548Slco2a11.33E-081.09E-06ENSMUSG0000039405Prss231.41E-078.33E-06ENSMUSG0000044337Ackr38.18E-097.03E-07ENSMUSG0000025608Podxl9.00E-062.65E-04ENSMUSG0000051022Hs3st13.31E-032.81F-02	1.402 1.239 1.022
ENSMUSG0000039405Prss231.41E-078.33E-06ENSMUSG0000044337Ackr38.18E-097.03E-07ENSMUSG0000025608Podxl9.00E-062.65E-04ENSMUSG0000051022Hs3st13.31E-032.81F-02	0.853 2.286 1.134
ENSMUSG00000051022 Hs3st1 3.31E-03 2.81F-02	1.232 1.377 1.060
ENSMUSG00000044317 Gpr4 7.48E-07 3.42E-05	0.513
ENSMUSG0000004951 Hspb1 1.87E-16 1.06E-13 ENSMUSG00000030208 Emp1 4.62E-02 1.80E-01 ENSMUSG00000038811 Gngt2 3.22E-11 5.38E-09	0.619
ENSMUSG00000035863Palm7.89E-049.45E-03ENSMUSG00000039899Fgl23.19E-127.78E-10ENSMUSG00000032470Mras6.61E-062.06E-04	0.721 1.658 0.609
ENSMUSG0000001175Calm13.77E-093.44E-07ENSMUSG00000038816Ctnnal15.23E-051.12E-03ENSMUSG00000009687Exvd54.61E-162.33E-13	0.726 1.015 1.219
ENSMUSG00000026785 Pkn3 1.82E-07 1.06E-05 ENSMUSG00000030342 Cd9 7.30E-14 2.38E-11	1.283
ENSMUSG0000002944Cd361.65E-031.68E-02ENSMUSG0000015850Adamtsl43.45E-021.50E-01ENSMUSG00000041731Pgm52.52E-056.08E-04	0.915 0.718 1.047
ENSMUSG0000026202 Tuba4a 3.59E-07 1.91E-05 ENSMUSG00000001435 Col18a1 1.00E-05 2.86E-04 ENSMUSG00000032231 Apya2 1.43E-10 2.00E-08	0.839 1.159 1.338
ENSMUSG00000021943 Gdf10 1.39E-03 1.49E-02 ENSMUSG00000028776 Tinagl1 3.46E-05 7.97E-04	0.610
ENSMUSG0000046768Rhoj2.53E-071.42E-05ENSMUSG0000003849Nqo15.89E-061.87E-04ENSMUSG00000025856Pdgfa8.93E-085.70E-06	0.998 0.962 0.853
ENSMUSG0000029095 Ablim2 6.65E-05 1.36E-03 ENSMUSG00000071379 Hpcal1 4.94E-07 2.45E-05	1.134 0.732
ENSMUSG0000002504 SIC9372 8.61E-08 5.58E-06 ENSMUSG00000027111 Itga6 2.38E-05 5.80E-04 ENSMUSG00000027800 Tm4sf1 7.22E-03 5.00E-02	0.718 0.529
ENSMUSG0000016024Lbp3.49E-061.25E-04ENSMUSG0000056501Cebpb6.91E-051.40E-03ENSMUSG00000040659Efhd21.24E-144.72E-12	1.454 0.623 1.269
ENSMUSG00000017652 Cd40 2.32E-03 2.18E-02 ENSMUSG00000028152 Tspan5 4.63E-04 6.31E-03 ENSMUSG00000028152 Dataset 7.12E-15 2.05E-12	0.634
ENSMUSG00000037060 Prkcdbp 7.13E-15 3.05E-12 ENSMUSG00000001552 Jup 1.13E-05 3.20E-04 ENSMUSG00000019890 Nts 1.94E-05 4.91E-04	1.318 0.845 1.011
ENSMUSG0000031841 Cdh13 2.45E-03 2.26E-02 ENSMUSG00000032802 Srxn1 5.24E-06 1.73E-04 ENSMUSG000000374264 Enda 5.03E-07 2.80E-05	1.537 0.870
ENSMUSG00000074364 End2 5.93E-07 2.80E-05 ENSMUSG00000056025 Clca3a1 3.62E-04 5.26E-03 ENSMUSG00000023990 Tfeb 1.03E-03 1.17E-02	0.948 0.651 0.646
ENSMUSG0000006445 Epha2 1.96E-05 4.95E-04 ENSMUSG00000038112 AW551984 4.31E-06 1.46E-04 ENSMUSG00000032369 Blscr1 4.17E.06 1.43E.04	0.556 1.141
ENSMUSG00000058672 Tubb2a 1.20E-10 1.76E-08 ENSMUSG00000035373 Ccl7 2.44E-04 3.84E-03	1.092 0.639
ENSMUSG00000041189Chrnb14.99E-051.08E-03ENSMUSG00000049775Tmsb4x1.62E-102.24E-08ENSMUSG00000018906P4ha26.73E-062.09E-04	0.842 1.162 0.927
ENSMUSG00000048807Slc35e44.51E-046.19E-03ENSMUSG00000047714Ppp1r26.13E-047.78E-03	0.689
ENSMUSG0000038400Pmepa11.81E-054.67E-04ENSMUSG0000032698Lmo22.82E-044.29E-03ENSMUSG0000090958Lrrc322.14E-102.71E-08	0.699 0.589 1.122
ENSMUSG00000031538 Plat 1.67E-03 1.70E-02 ENSMUSG0000004044 Ptrf 1.04E-04 1.94E-03	0.994
ENSMUSG00000041959\$100a101.56E-091.53E-07ENSMUSG00000022265Ank2.70E-032.43E-02ENSMUSG00000045730Adrb21.88E-043.13E-03	0.893 0.781 0.790
ENSMUSG0000030154 Klrb1f 5.55E-05 1.19E-03 ENSMUSG00000042745 Id1 9.13E-06 2.67E-04 ENSMUSG00000044022 Code144 5.55E-05 1.19E-03	1.256 1.292
ENSIGNOUUUU44033CCdC1419.01E-041.05E-02ENSMUSG0000029552Tes1.03E-112.04E-09ENSMUSG0000025510Cd1516.87E-034.82F-02	1.137 0.784 0.626
ENSMUSG0000040511 Pvr 6.91E-05 1.40E-03 ENSMUSG00000015745 Plekho1 8.42E-04 9.96E-03 ENSMUSG0000004686 Colora	0.813
ENSIGUOUUUU94686CCl21a7.19E-108.19E-08ENSMUSG00000022433Csnk1e4.61E-033.60E-02ENSMUSG0000024659Anxa13.73E-093.43F-07	3.797 0.518 1.543
ENSMUSG0000026558 Uck2 9.95E-04 1.14E-02 ENSMUSG00000036398 Ppp1r11 8.73E-08 5.60E-06 ENSMUSG00000030132 Ptrue	0.623
ENSIMUSGUUUUU30122Ptms1.77E-042.98E-03ENSMUSG0000026435Slc45a31.31E-031.42E-02ENSMUSG00000019139Isyna16.07F-047.72E-03	0.584 0.848 0.610
ENSMUSG0000034684 Sema3f 2.24E-05 5.49E-04 ENSMUSG00000030522 Mtmr10 8.60E-04 1.01E-02	0.963 0.591
ENSIMUSGUUUUUU41313SIc7a15.92E-051.24E-03ENSMUSG00000058569Tmed94.11E-061.41E-04ENSMUSG0000006356Crip24.65E-094.21E-07	0.724 0.861 0.769
ENSMUSG0000046223 Plaur 3.08E-05 7.19E-04 ENSMUSG0000002233 Rhoc 7.84E-06 2.38E-04	0.974 0.521
ENSIMUSG0000024486Hbegf5.77E-047.39E-03ENSMUSG0000062421Arf21.41E-065.86E-05ENSMUSG00000023067Cdkn1a6.65E-073.09E-0E	0.702 0.766 0.694
ENSMUSG0000030695 Aldoa 1.74E-05 4.53E-04 ENSMUSG00000070934 Rraga 8.29E-07 3.74E-05	0.567 0.745
LINSINIOSGUUUUU2/784Ppm1I1.28E-053.56E-04ENSMUSG0000014158Trpv41.02E-041.92E-03ENSMUSG0000019590Cyb5614.45E-061.50F-04	0.713 0.712 1.131
ENSMUSG0000026796 Fam129b 8.55E-09 7.31E-07 ENSMUSG00000019194 Scn1b 1.31E-02 7.60E-02 ENSMUSG00000021814 Amor7 5.55E-09 5.55E-09	0.974
ENSMUSG0000057530 Ece1 9.19E-06 2.68E-04 ENSMUSG00000075702 Selm 3.94E-03 3.22E-02 ENSMUSG00000075702 Selm 5.56E-07 2.67E-05	0.652 0.715 0.736
ENSMUSG0000023224Serping11.67E-066.76E-05ENSMUSG0000063856Gpx12.54E-043.96E-03ENSMUSG00000015932Dstn5.54E-061.80E-04	0.733
ENSMUSG0000002980Bcam5.54E-061.80E-04ENSMUSG00000018217Pmp228.70E-035.71E-02	0.640 0.659 0.523
ENSMUSG0000021871Pnp7.51E-049.12E-03ENSMUSG0000020248Nfyb4.17E-045.86E-03ENSMUSG00000034361Cppe28.845.062.625.04	0.535
ENSMUSG00000034501Cpriez8.84E-062.62E-04ENSMUSG00000038650Rnh12.06E-055.16E-04ENSMUSG00000025597Klhl45.53E-034.11E-02	0.644 0.523 0.525
ENSMUSG0000019173Rab5c4.39E-033.47E-02ENSMUSG0000001946Esam2.68E-061.00E-04ENSMUSG00000022564Grina5.61E-047.21E-02	0.893
ENSMUSG00000022564 Grina 5.61E-04 7.24E-03 ENSMUSG00000034432 Cops8 5.72E-05 1.21E-03 ENSMUSG00000020334 Slc22a4 4.78E-03 3.70E-02	0.579 0.571 0.690
ENSMUSG0000062825 Actg1 9.21E-06 2.68E-04 ENSMUSG0000037465 Klf10 6.84E-03 4.81E-02 ENSMUSC00000047547 Chb 7.77E-04 9.32E-03	0.625
ENSMUSG00000047547 Citb 7.77E-04 9.33E-03 ENSMUSG00000021493 Pdlim7 1.96E-06 7.70E-05 ENSMUSG00000072620 Slfn2 8.97E-07 3.99E-05	0.552 0.733 0.835
ENSMUSG0000039911 Spsb1 1.18E-04 2.13E-03 ENSMUSG0000042734 Ttc9 1.16E-07 7.03E-06 ENSMUSG00000202323 H=1 4.36E-02 2.69E-02	0.577
ENSMUSG0000020737 Hn1 4.76E-03 3.69E-02 ENSMUSG0000032135 Mcam 3.44E-04 5.04E-03 ENSMUSG00000029126 Nsg1 5.85E-03 4.29E-02	0.527 0.546 0.755
ENSMUSG0000038387 Rras 5.87E-06 1.87E-04 ENSMUSG00000054641 Mmrn1 5.34E-04 7.02E-03 ENSMUSG00000020602 Dtv14 5.34E-04 7.02E-03	0.509 1.563
ENSMUSG0000025005Dixi1.23E-027.27E-02ENSMUSG00000035268Pkig1.20E-065.07E-05ENSMUSG0000003752Itpkc4.18E-059.36E-04	0.733 0.634 0.745
ENSMUSG0000015837 Sqstm1 6.70E-03 4.74E-02 ENSMUSG0000001964 Emd 8.44E-03 5.60E-02 ENSMUSG00000025372 Bajap 2 1.605.02 1.755.02	0.582
ENSMUSG0000007041 Clic1 2.61E-04 4.04E-03 ENSMUSG00000047407 Tgif1 1.85E-05 4.73E-04	0.519 0.567 0.645
ENSMUSG0000023905Tnfrsf12a4.42E-072.24E-05ENSMUSG0000027954Efna19.40E-062.72E-04ENSMUSG0000052397Ezr3.08E.061.12E.04	0.879 0.872 0.560
ENSMUSG0000090841 Myl6 3.06E-04 4.59E-03 ENSMUSG00000042675 Ypel3 2.37E-04 3.75E-03	0.584 0.607
ENSMUSG00000050931 Sgms2 2.54E-05 6.10E-04	1.009 1.418 0.610
ENSMUSG0000046916 Mvct1 3.34E-08 2.39E-06 3.23E-03 2.76E-02	0.553
ENSIVIUSGUUUUU31391L1cam3.34E-082.39E-06ENSMUSG00000046916Myct13.23E-032.76E-02ENSMUSG00000060860Ube2s2.25E-032.14E-02ENSMUSG0000001493Meox12.19E-043.53E-03	0.519 0.619 0.619
ENSIGNOUCOUU31391 L1cam 3.34E-08 2.39E-06 ENSMUSG00000046916 Myct1 3.23E-03 2.76E-02 ENSMUSG00000060860 Ube2s 2.25E-03 2.14E-02 ENSMUSG00000001493 Meox1 2.19E-04 3.53E-03 ENSMUSG00000005514 Por 1.23E-02 7.27E-02 ENSMUSG00000008393 Carhsp1 7.42E-05 1.47E-03 ENSMUSG00000056214 Pard6g 7.98E-03 5.36E-02	0.975 0.671
EINSIVIUSGUUUUU31391L1cam3.34E-082.39E-06ENSMUSG0000046916Myct13.23E-032.76E-02ENSMUSG00000060860Ube2s2.25E-032.14E-02ENSMUSG0000001493Meox12.19E-043.53E-03ENSMUSG0000005514Por1.23E-027.27E-02ENSMUSG0000008393Carhsp17.42E-051.47E-03ENSMUSG00000056214Pard6g7.98E-035.36E-02ENSMUSG00000026249Serpine23.84E-045.49E-03ENSMUSG00000046731Kctd111.45E-031.53E-02	0.504
ENSIMUSGUUUUUU31391L1cam3.34E-082.39E-06ENSMUSG0000046916Myct13.23E-032.76E-02ENSMUSG00000060860Ube2s2.25E-032.14E-02ENSMUSG0000001493Meox12.19E-043.53E-03ENSMUSG0000005514Por1.23E-027.27E-02ENSMUSG0000005514Por1.23E-051.47E-03ENSMUSG00000056214Pard6g7.98E-035.36E-02ENSMUSG00000026249Serpine23.84E-045.49E-03ENSMUSG00000026249Serpine23.84E-046.72E-03ENSMUSG00000021377Dek5.04E-046.72E-03ENSMUSG00000074457S100a165.31E-061.74E-04ENSMUSG00000032261Sh3bgrl25.22E-033.96E-02	0.723 0.545
ENSIGUEUUUU31391L1cam3.34E-082.39E-06ENSMUSG0000046916Myct13.23E-032.76E-02ENSMUSG0000060860Ube2s2.25E-032.14E-02ENSMUSG0000001493Meox12.19E-043.53E-03ENSMUSG0000005514Por1.23E-027.27E-02ENSMUSG0000005514Por1.23E-031.47E-03ENSMUSG00000056214Pard6g7.98E-035.36E-02ENSMUSG0000026249Serpine23.84E-045.49E-03ENSMUSG0000026249Serpine23.84E-046.72E-03ENSMUSG0000021377Dek5.04E-046.72E-03ENSMUSG0000074457S100a165.31E-061.74E-04ENSMUSG000002261Sh3bgrl25.22E-033.96E-02ENSMUSG000002261Sh3bgrl25.22E-033.96E-02ENSMUSG0000020402Vdac18.13E-062.45E-04ENSMUSG00000026300Elovl18.72E-073.91E-05	0.723 0.545 0.782 0.525
ENSINUSGUUUUUU31391L1cam3.34E-082.39E-06ENSMUSG0000046916Myct13.23E-032.76E-02ENSMUSG0000060860Ube2s2.25E-032.14E-02ENSMUSG000000514Por1.23E-027.27E-02ENSMUSG0000005514Por1.23E-027.27E-02ENSMUSG0000005514Por1.23E-035.36E-03ENSMUSG00000056214Pard6g7.98E-035.36E-02ENSMUSG00000026249Serpine23.84E-045.49E-03ENSMUSG00000026249Serpine23.84E-046.72E-03ENSMUSG00000021377Dek5.04E-046.72E-03ENSMUSG0000002427S100a165.31E-061.74E-04ENSMUSG0000002261Sh3bgrl25.22E-033.96E-02ENSMUSG0000002261Sh3bgrl25.22E-033.96E-02ENSMUSG0000002261Sh3bgrl25.22E-033.96E-02ENSMUSG00000022649Elovl18.72E-073.91E-05ENSMUSG00000022640Vdac18.13E-062.45E-04ENSMUSG0000002786Alas17.54E-049.15E-03ENSMUSG00000021759Ppap2a9.32E-074.11E-05ENSMUSG00000021759Ppap2a9.32E-074.11E-05ENSMUSG00000021759Ppap2a7.28E-048.91E-03	0.723 0.545 0.782 0.525 0.625 1.192 0.725
ENSIMUSGUUUUU31391L1cam3.34E-082.39E-06ENSMUSG0000046916Myct13.23E-032.76E-02ENSMUSG00000060860Ube2s2.25E-032.14E-02ENSMUSG00000001493Meox12.19E-043.53E-03ENSMUSG00000005514Por1.23E-027.27E-02ENSMUSG0000005514Por1.23E-035.36E-02ENSMUSG00000055214Pard6g7.98E-035.36E-02ENSMUSG00000026249Serpine23.84E-045.49E-03ENSMUSG00000026249Serpine23.84E-046.72E-03ENSMUSG0000021377Dek5.04E-046.72E-03ENSMUSG0000021377Dek5.22E-033.96E-02ENSMUSG0000021377Dek5.21E-061.74E-04ENSMUSG000002261Sh3bgrl25.22E-033.96E-02ENSMUSG0000020402Vdac18.13E-062.45E-04ENSMUSG00000021759Ppap2a9.32E-074.11E-05ENSMUSG00000021759Ppap2a9.32E-074.11E-05ENSMUSG00000021759Ppap2a7.28E-048.91E-03ENSMUSG0000006301Tmbim12.37E-043.75E-03ENSMUSG000000379601110007C09Rik5.07E-051.09E-03ENSMUSG00000037960Thbint 12.37E-043.75E-03ENSMUSG000000379601110007C09Rik5.07E-051.09E-03	0.723 0.545 0.782 0.525 0.625 1.192 0.725 0.570 0.671
ENSMUSSGUUUUU31391 L1cam 3.34E-08 2.39E-06 ENSMUSG0000046916 Myct1 3.23E-03 2.76E-02 ENSMUSG00000060860 Ube2s 2.25E-03 2.14E-02 ENSMUSG0000001493 Meox1 2.19E-04 3.53E-03 ENSMUSG00000005514 Por 1.23E-02 7.27E-02 ENSMUSG00000055214 Pard6g 7.98E-03 5.36E-02 ENSMUSG00000026249 Serpine2 3.84E-04 5.49E-03 ENSMUSG0000026249 Serpine2 3.84E-04 6.72E-03 ENSMUSG00000026249 Serpine2 3.84E-04 6.72E-03 ENSMUSG00000026249 Serpine2 3.84E-04 6.72E-03 ENSMUSG00000021377 Dek 5.04E-04 6.72E-03 ENSMUSG00000021377 Dek 5.22E-03 3.96E-02 ENSMUSG00000021377 Dek 5.22E-03 3.96E-02 ENSMUSG0000002402 Vdac1 8.13E-06 2.45E-04 ENSMUSG00000021759 Ppap2a 9.32E-07 4.11E-05 ENSMUSG00000021759 Ppap2a 9.32E-03 8.91E-03 ENSMUSG00000021759 Ppap2a 7.28	0.723 0.545 0.782 0.525 0.625 1.192 0.725 0.570 0.671 1.198 0.843
ENSMUSSGUUUUUU31391 L1cam 3.34E-08 2.39E-06 ENSMUSG0000046916 Myct1 3.23E-03 2.76E-02 ENSMUSG00000060860 Ube2s 2.25E-03 2.14E-02 ENSMUSG0000001493 Meox1 2.19E-04 3.53E-03 ENSMUSG00000005514 Por 1.23E-02 7.27E-02 ENSMUSG0000008393 Carhsp1 7.42E-05 1.47E-03 ENSMUSG00000026249 Serpine2 3.84E-04 5.49E-03 ENSMUSG00000021377 Dek 5.04E-04 6.72E-03 ENSMUSG00000024673 Kctd11 1.45E-03 1.53E-02 ENSMUSG00000024177 Dek 5.04E-04 6.72E-03 ENSMUSG0000002402 Vdac1 8.13E-06 2.45E-04 ENSMUSG0000002402 Vdac1 8.72E-07 3.91E-05 ENSMUSG00000021759 Ppap2a 9.32E-07 4.11E-05 ENSMUSG00000021759 Ppap2a 7.28E-04 8.91E-03 ENSMUSG0000003175 Alas1 7.54E-04 9.15E-03 ENSMUSG0000003175 Phipyp1 2.56E-04	0.723 0.545 0.782 0.525 0.625 1.192 0.725 0.570 0.671 1.198 0.843 0.560 0.594 0.542
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ENSMUSSUUUUUUUUUUUUUUUUUUUUUUUUUUUUUUUUU	0.723 0.545 0.782 0.525 0.625 1.192 0.725 0.570 0.671 1.198 0.843 0.560 0.594 0.542 0.524 1.226 0.647 0.619 0.689
ENSMUSGUUUUUJ1391 L1cam 3.34E-08 2.39E-06 ENSMUSG0000046916 Myct1 3.23E-03 2.76E-02 ENSMUSG0000001493 Meox1 2.19E-04 3.53E-03 ENSMUSG00000005514 Por 1.23E-02 7.27E-02 ENSMUSG0000005514 Por 1.23E-03 5.36E-02 ENSMUSG00000056214 Pardóg 7.98E-03 5.36E-02 ENSMUSG000000626249 Serpine2 3.84E-04 5.49E-03 ENSMUSG00000026249 Serpine2 3.84E-04 6.72E-03 ENSMUSG00000046731 Kctd11 1.45E-03 1.53E-02 ENSMUSG00000021377 Dek 5.04E-04 6.72E-03 ENSMUSG0000002402 Vdac1 8.13E-06 1.74E-04 ENSMUSG0000002402 Vdac1 8.72E-07 3.91E-05 ENSMUSG00000024759 Ppap2a 9.32E-07 4.11E-05 ENSMUSG00000021759 Ppap2a 9.32E-07 4.11E-05 ENSMUSG00000032766 Alas1 7.54E-04 9.15E-03 ENSMUSG0000000317mbim1 2.37E-04 3.75E-03	0.723 0.545 0.782 0.525 0.625 1.192 0.725 0.570 0.671 1.198 0.843 0.560 0.594 0.524 1.226 0.647 0.647 0.619 0.689 0.503 0.503 0.922
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