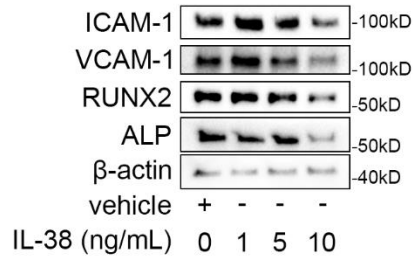
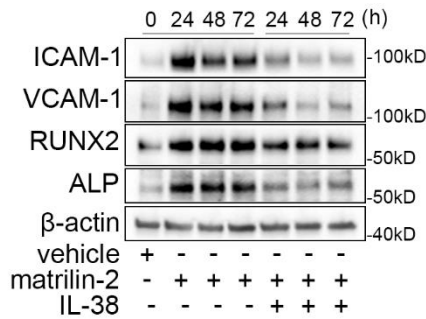


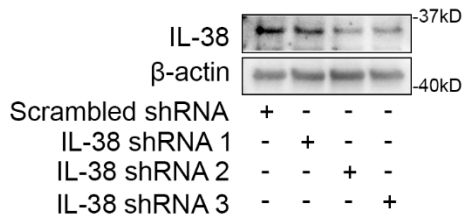
Supplemental Data:



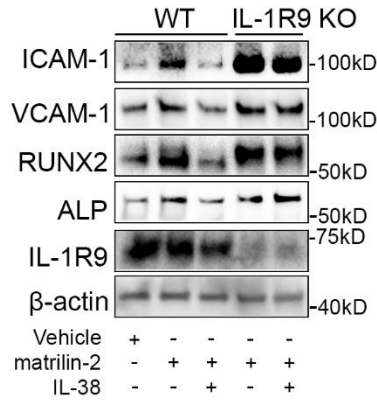
Supplemental Figure 1. Recombinant IL-38 (10 ng/mL) reduces spontaneous expression of inflammation and osteogenic mediators in human AVICs from CAVD valves. n = 2 donors.



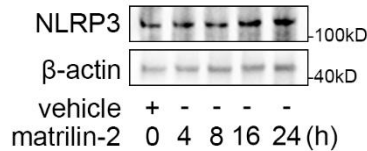
Supplemental Figure 2. IL-38 (10 ng/mL) suppresses matrilin-2 (2 μg/mL)-induced inflammatory and osteogenic responses in human AVICs from non-CAVD valves in a time-dependent fashion. n = 2 donors.



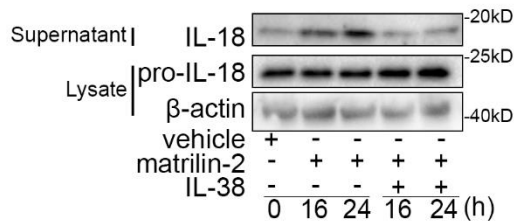
Supplemental Figure 3. Knockdown using shRNA reduces IL-38 protein level in human AVICs from non-CAVD valves. n = 1 donor.



Supplemental Figure 4. IL-38 (10 ng/mL) fails to reduce the inflammatory and osteogenic responses to matrilin-2 (2 μg/mL) in AVICs from IL-1R9 KO mice. n = 2 mice per group.



Supplemental Figure 5. Matrilin-2 (2 μg/mL) increases NLRP3 inflammasome expression in human AVICs from non-CAVD valves. n = 2 donors.



Supplemental Figure 6. IL-38 (10 ng/mL) reduces IL-18 secretion in human AVICs exposed to matrilin-2 (2 μg/mL). n = 2 donors.

Supplemental Tables:

Supplemental Table 1. gRNA and PCR primer sequences for confirmation of IL-38 KO.

Purpose	Sequence	Vector ID
gRNA before <i>Il38</i> Exon 1	GCGAGAGAACAGTTACCGAATGG (Matches forward strand)	VB180116-1110yca
gRNA after <i>Il38</i> Exon 4	TTCAATATTGGTAGGCACCCCGG (Matches forward strand)	VB180116-1112eat
Identification of IL-38 KO (presence of short product indicates removal of genomic)	Forward: CCCATGCCGTAGAGCACATCTGT Reverse: GGTCATCTTGTGCTGTAGCTCTGC	

DNA including <i>Il38</i> exons 1-4)		
PCR Identification of WT	Forward: TCCAGGGTACCTGAGCTTCA Reverse: GTCTTCTCATGAGGTAATTGAGGA TGT	
PCR Identification of <i>Il38</i> KO Presence indicates <i>Il38</i> deficiency	Forward: CTGGCTCATTGCTTGTAACACTAC Reverse: AGGAGAATCCCTAGATGTCTTTCC A	

Supplemental Table 2. gRNA and PCR primer sequences for generation and confirmation of IL-1R9 KO.

Purpose	Sequence	Vector ID
gRNA before <i>Il1rap1l</i> Exon 3	ACATTCTGTCTAACGTTCCCAGG (Matches forward strand)	VB180201-1090ckj
gRNA after <i>Il1rap1l</i> Exon 3	TATCGGGTATAAGATCTCTCTGG (Matches forward strand)	VB180201-1091xnv
Identification of IL-1R9 KO (presence of short product indicates removal of genomic DNA including <i>Il1rap1l</i> exons 3)	Forward: CTAATTCCAAATACCCATCTCCAA ACACT Reverse: AAACAAGGTTGCTCTCTCTCTCCC AG	
PCR Identification of WT	Forward: CCTCTTCCTGTTCCCCACATATGTA Reverse: CCAGTTGTTTGGGACCCACAT	
PCR Identification of IL-1R9 KO Presence indicates IL-1R9 deficiency	Forward: GCAATACAACAGCCCCTTGG Reverse: ACAAATTGGAAAGGAAGAAGTCA AGGT	

Supplemental Table 3. Aortic valve donor demographics

Donor Number	Gender	Age (years)	Diagnosis
Normal 1	F	60	Ischemic Cardiomyopathy

Normal 2	F	65	Ischemic Cardiomyopathy
Normal 3	F	68	Non-ischemic Cardiomyopathy
Normal 4	M	58	Non-ischemic dilated cardiomyopathy
Normal 5	M	60	Non-ischemic Cardiomyopathy
Normal 6	M	66	Ischemic Cardiomyopathy
Diseased 1	F	65	Aortic stenosis
Diseased 2	F	68	Aortic stenosis
Diseased 3	F	67	Aortic stenosis
Diseased 4	M	62	Aortic stenosis
Diseased 5	M	68	Aortic stenosis
Diseased 6	M	59	Aortic stenosis