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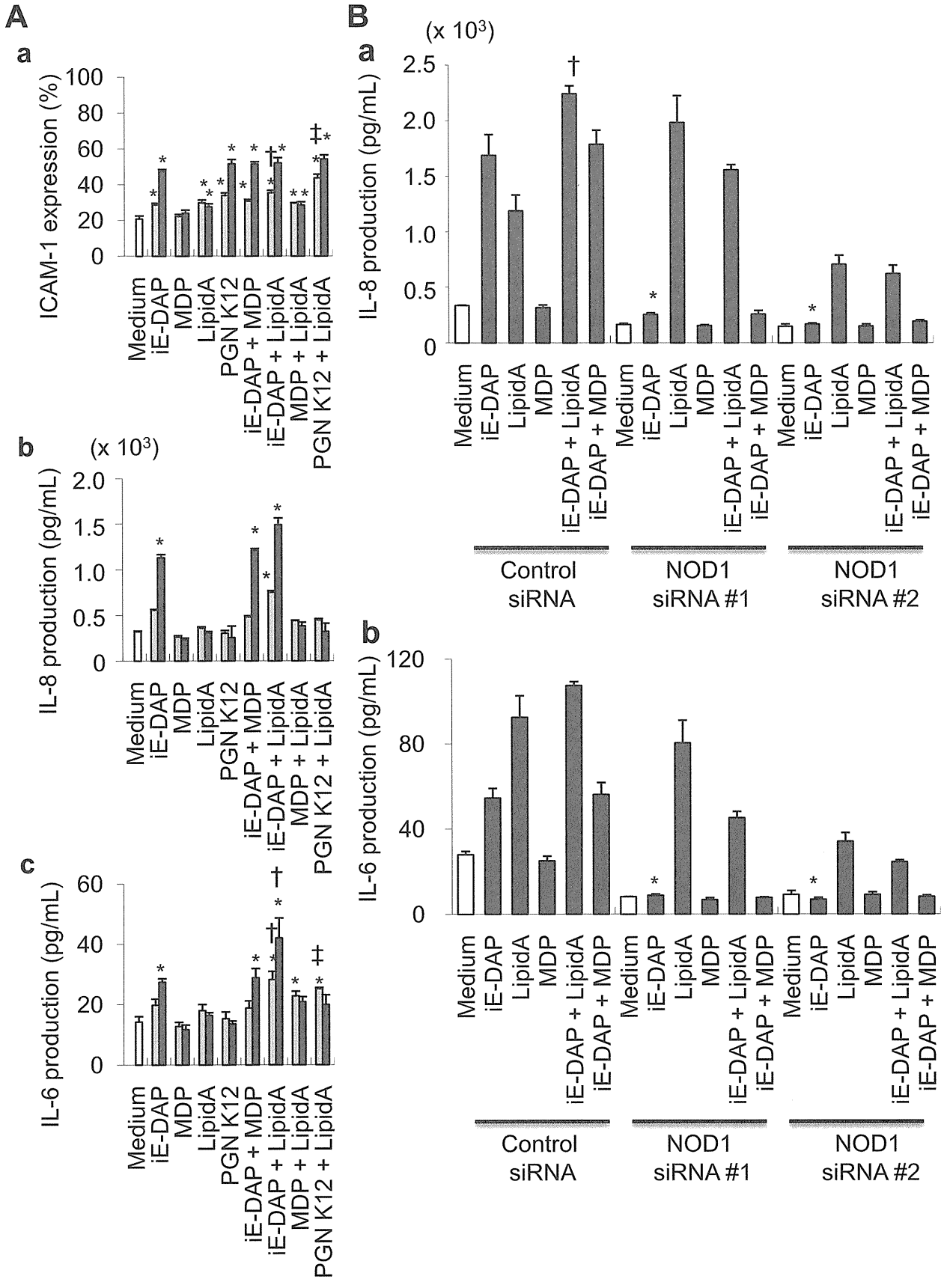
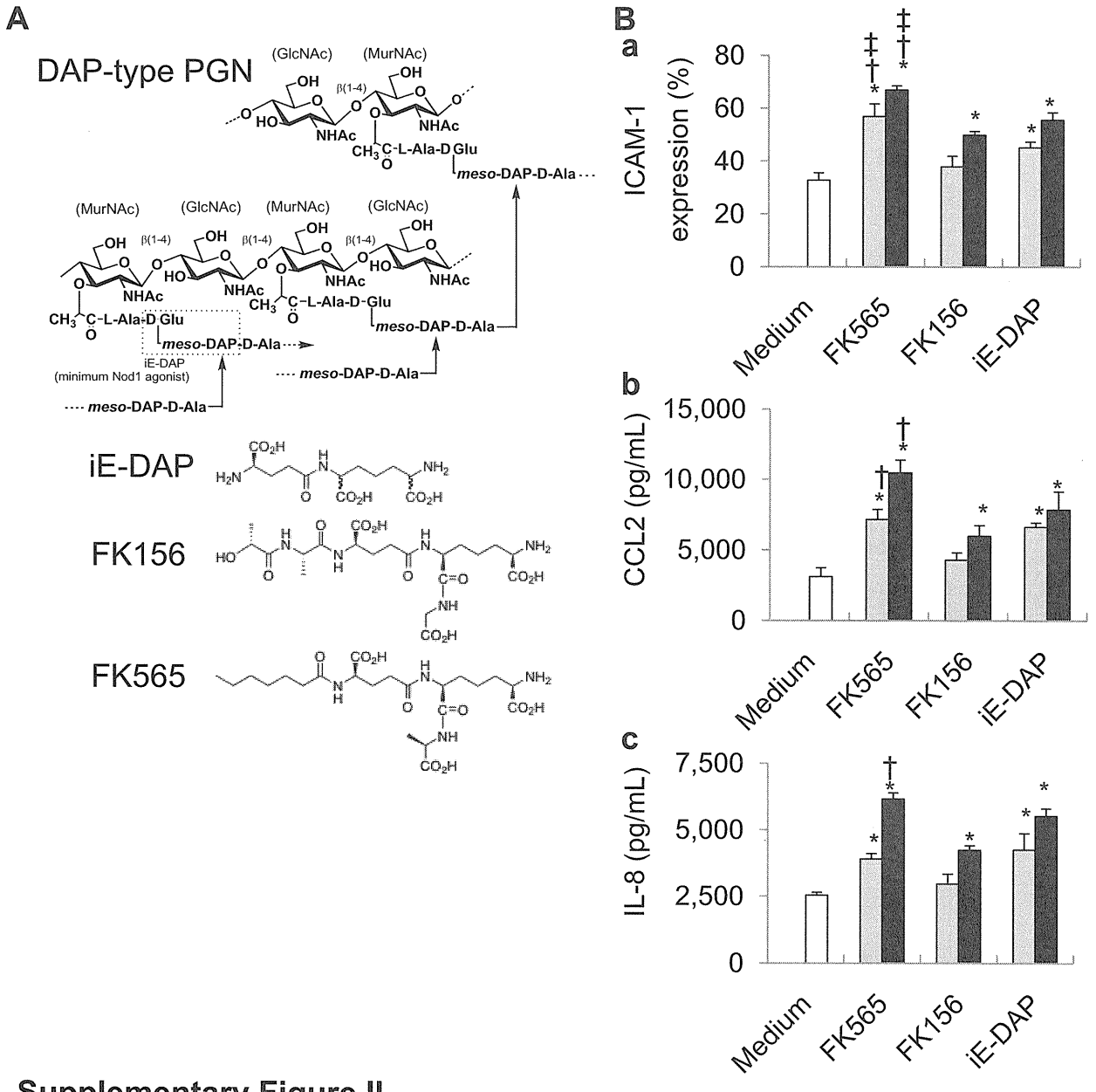
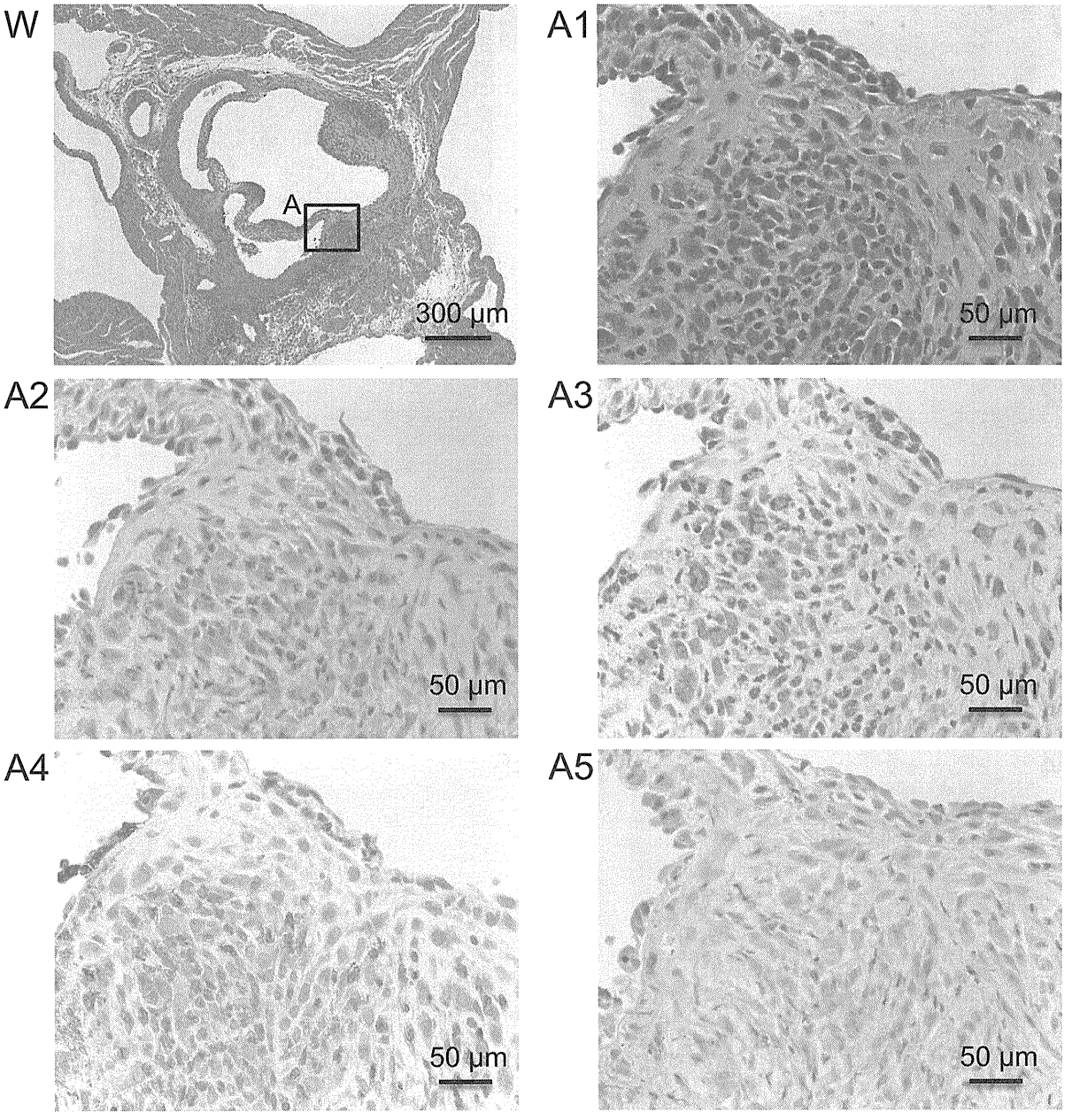
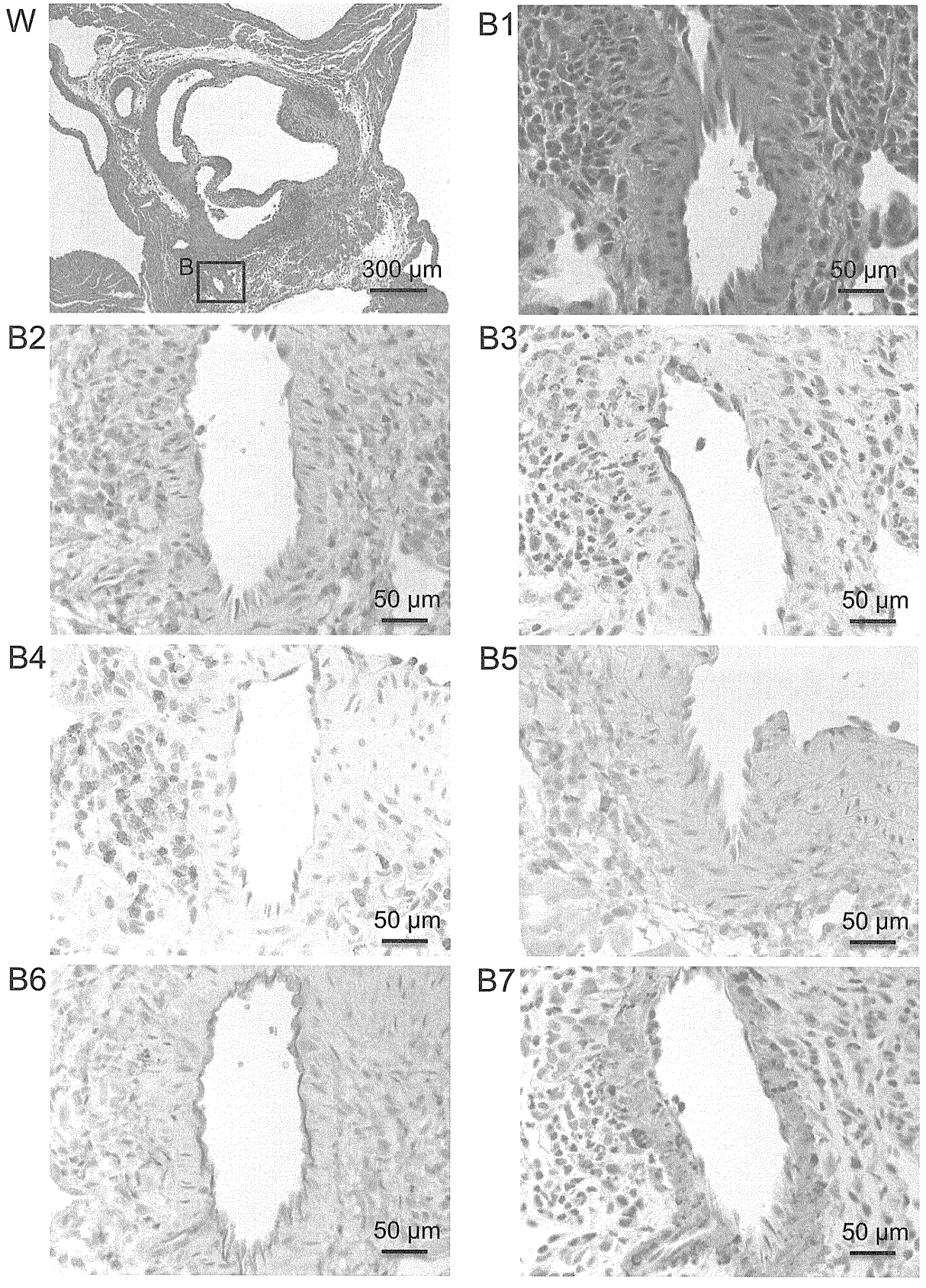


Supplementary Figure I

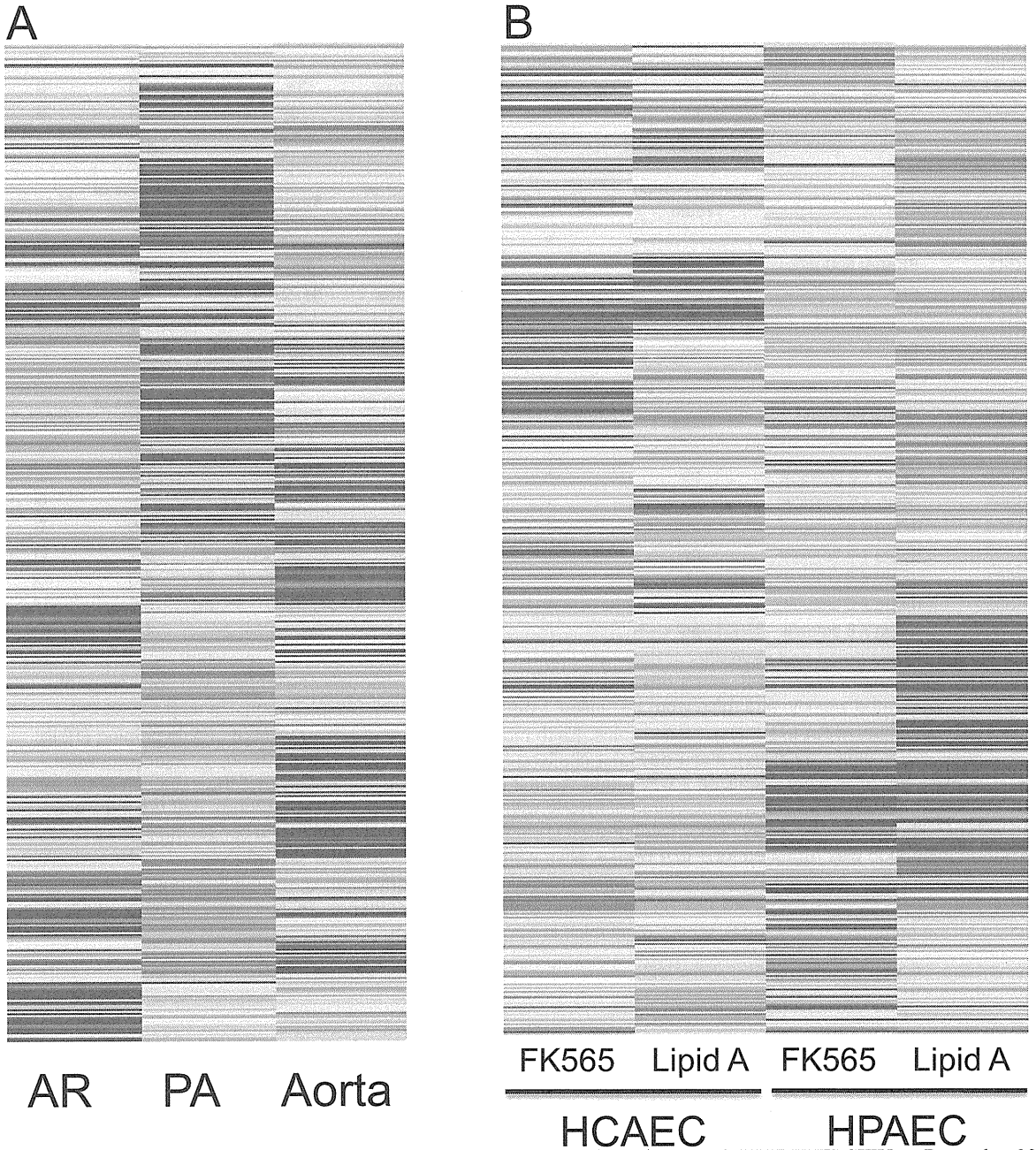


Supplementary Figure II





Supplementary Figure III



Supplementary Figure IV

Supplementary Table I. Induction of coronary arteritis by microbial reagents.

A

Reagents	Dose (/mouse)	Administration route	Priming (LPS ip)	Number of Administration	Severity of CA	Incidence of CA+No./	SI score
None	-	-	20 or 50μg/w	4 times	-, -, -	0/3	0
None	-	-	100μg/w	4 times	-, -, -	0/3	0
Zymosan	500μg/w	sc	20μg	4 times	-, -, -	0/3	0
OK432	1KE/w	sc	20μg	4 times	-, -, -	0/3	0
PGN K12	500μg/w	sc	20μg	4 times	-, -, -	0/3	0
MDP	500μg/w	sc	20μg	4 times	-, -, -	0/3	0
FK565	500μg/w	sc	20μg	4 times	3+, 3+, 3+	3/3	9
FK565	500μg/w	sc	-	4 times	+, -, -	1/3	1
FK565	200μg/w	sc	20μg	4 times	+, -, -	1/3	1
FK565	100μg/w	sc	20μg	4 times	-, -, -	0/3	0
FK565+MDP	500μg, 500μg/w	sc	20μg	4 times	3+, 3+, 3+	3/3	9
FK565+MDP	200μg, 200μg/w	sc	20μg	4 times	3+, 2+, -	2/3	5
FK565+MDP	100μg, 100μg/w	sc	20μg	4 times	+, +, -	2/3	2

B

Mouse	Reagent/ Dose (/mouse)	Administration route	Priming (LPS ip)	Number of Administration	Severity of CA	Incidence of CA+No./	SI score
SCID	-	-	+	4 times	-, -, -	0/3	0
SCID	FK565/ 500μg/w	sc	-	4 times	2+, +, - , -, -	2/5	3
SCID	FK565/ 500μg/w	sc	+	4 times	3+, 2+, +, +, +	5/5	8
Nod1 $^{-/-}$	-	-	+	4 times	-, -, -	0/3	0
Nod1 $^{-/-}$	FK565/ 500μg/w	sc	+	4 times	-, -, -, -, -	0/5	0

C

Reagents	Dose (/mouse)	Administration route	Priming (LPS ip)	Duration of Administration	Severity of CA	Incidence of CA+No./	SI score
-	-	-	+	4 w	-, -, -, -, -	0/5	0
FK565	25μg x 6 times/w	po	+	1 w	+, +, -, -, -	2/5	2
FK565	50μg x 6 times/w	po	+	1 w	-, -, -, -, -	0/5	0
FK565	100μg x 6 times/w	po	+	1 w	2+, 2+, +, +, +	5/5	7
FK565	100μg x 6 times/w	po	+	2 w	3+, 3+, 2+, 2+, +	5/5	11
FK565	100μg x 6 times/w	po	+	3 w	3+, 3+, 2+, 2+, 2+	5/5	12
FK565	100μg x 6 times/w	po	+	4 w	3+, 3+, 3+, 3+, 2+	5/5	14
FK565	100μg x 6 times/w	po	-	4 w	3+, 3+, 3+, 2+,-	4/5	11

Panel A shows the incidence and severities of coronary arteritis (CA) in response to various microbial reagents. BALB/c mice were primed with or without LPS, and 1 day later the mice were subcutaneously challenged with each reagent. Injections were repeated weekly, and mice were sacrificed 1 week after the last administration. Panel B shows the incidence and severities of CA in SCID or Nod1$^{-/-}$ mice. Each mouse was primed with or without LPS ip priming (10μg: dose reduction due to high sensitivity), and 1 day later challenged with or without sc FK565 (500μg). Injections were repeated weekly, and mice were sacrificed 1 week after the last administration. Panel C shows the induction of CA by various doses and durations of oral administration of FK565 with or without LPS ip priming (20μg). BALB/c mice were primed with or without LPS and 1 day later challenged with oral administration of FK565 for 6 consecutive days (1 week course). Administration was repeated for 1 to 4 weeks. Mice were sacrificed 1day after last administration. No vasculitis was observed in NOD1$^{-/-}$ mice after oral administration of FK565. ip = intraperitoneal; sc = subcutaneous; po = per os; w: week, KE = Klinische Einheit units; OK432 = penicillin-killed streptococcus pyogenes; PGN = peptidoglycan. SI score is calculated by the summation of severity scores of all mice in each experiment.

Supplementary Table II. Top 10 genes expressed in aortic root after oral administration of FK565 with or without LPS priming *in vivo*.

			Aortic root									Pulmonary artery									Aorta									Spleen								
			LPS			FK565			LPS+FK565			LPS			FK565			LPS+FK565			LPS			FK565			LPS+FK565			LPS			FK565			LPS+FK565		
Category	Symbol	Rank	day2	day4	day7	day2	day4	day7	day2	day4	day7	day2	day4	day7	day2	day4	day7	day2	day4	day7	day2	day4	day7	day2	day4	day7	day2	day4	day7	day2	day4	day7	day2	day4	day7	day2	day4	day7
All	Ccl5	1	5.1	4.5	1.5	**86.2**	**123.9**	**56.1**	108.7	62.9	34.0	0.8	0.8	0.3	3.5	**6.4**	3.0	3.2	3.7	2.1	17.2	9.5	3.7	**42.7**	**85.6**	**44.9**	78.7	87.0	47.9	0.4	1.5	1.1	0.9	3.3	2.8	1.1	2.5	1.3
	Arg1	2	8.9	4.4	2.5	**64.4**	**9.3**	4.6	192.8	27.5	7.1	0.5	0.5	0.4	2.7	0.7	0.5	17.7	6.0	0.8	9.9	9.0	2.6	**16.1**	**6.0**	3.7	48.4	14.9	4.6	3.6	1.2	2.1	**7.9**	1.8	0.6	19.1	4.3	3.1
	Ccl2	3	2.0	2.2	0.7	**34.4**	**36.7**	**15.2**	122.5	47.9	16.2	1.4	1.4	1.0	**10.1**	**11.6**	**8.2**	73.1	11.7	6.4	2.7	2.2	0.9	**20.3**	**26.2**	**12.7**	99.9	53.8	11.5	0.6	2.0	1.1	2.6	3.1	1.3	7.0	1.6	1.7
	Cxcl13	4	15.7	6.2	3.3	**32.1**	**8.2**	**17.0**	149.6	33.2	16.5	0.8	0.5	0.1	0.7	2.8	0.3	23.8	1.1	2.0	15.2	2.2	3.4	4.7	**8.0**	**6.2**	89.2	8.3	4.7	0.1	0.5	0.3	1.8	1.2	3.4	1.8	1.1	1.4
	Ccl8	5	4.3	4.2	2.3	**8.1**	**27.1**	**48.0**	4.1	92.5	36.1	5.4	6.4	2.0	**7.9**	**16.5**	**21.4**	3.7	12.4	13.5	2.9	3.4	0.9	2.5	**12.7**	**21.0**	1.6	8.2	7.2	1.5	2.2	2.3	0.9	3.8	0.8	1.0	1.6	0.8
	Il6	6	1.7	0.9	1.4	2.8	**12.9**	**15.3**	20.5	55.6	106.5	0.4	0.5	0.5	0.8	0.9	0.5	1.8	0.6	0.7	1.9	1.6	1.2	1.3	**7.7**	4.2	5.4	9.1	2.8	0.5	1.0	0.7	0.5	0.6	0.4	0.5	0.7	0.6
	Serpina3n	7	8.9	2.2	2.1	**25.4**	**17.6**	**14.5**	80.7	19.6	16.8	14.7	4.1	3.9	**42.1**	**6.7**	**9.9**	109.1	8.8	9.7	5.8	1.2	0.9	4.3	3.3	4.0	28.7	3.3	1.9	0.3	0.5	4.6	3.6	**5.9**	2.1	6.4	0.5	0.6
	Saa3	9	31.1	12.4	1.0	**35.8**	**25.5**	**20.6**	41.5	21.2	17.4	29.7	16.2	2.1	**24.0**	**11.4**	**16.1**	32.7	35.1	27.2	46.8	34.2	5.3	**28.9**	**25.1**	**42.2**	56.3	33.3	19.7	30.8	12.0	2.8	**21.3**	**15.7**	**9.8**	305.2	35.2	18.9
	Cfb	10	19.8	7.2	2.4	**22.4**	**24.2**	**21.8**	58.2	22.3	12.5	7.4	3.9	1.2	**7.4**	**7.8**	**8.5**	20.0	6.1	4.2	3.4	1.7	0.7	1.9	2.4	2.3	9.5	2.5	2.2	0.4	1.7	2.4	1.5	0.9	2.2	2.6	3.2	1.1
	Lcn2	11	24.9	1.9	0.5	**15.1**	**9.5**	**8.2**	82.3	15.4	17.9	34.5	3.7	1.5	**22.3**	**14.6**	**12.7**	89.1	8.0	1.5	3.8	0.5	0.1	0.9	0.8	0.6	9.5	2.1	0.5	0.2	0.4	2.4	0.9	1.2	0.8	5.1	2.6	2.1
Chemokine/cytokine	Ccl5	1	5.1	4.5	1.5	**86.2**	**123.9**	**56.1**	108.7	62.9	34.0	0.8	0.8	0.3	3.5	**6.4**	3.0	3.2	3.7	2.1	17.2	9.5	3.7	**42.7**	**85.6**	**44.9**	78.7	87.0	47.9	0.4	1.5	1.1	0.9	3.3	2.8	1.1	2.5	1.3
	Ccl2	3	2.0	2.2	0.7	**34.4**	**36.7**	**15.2**	122.5	47.9	16.2	1.4	1.4	1.0	**10.1**	**11.6**	**8.2**	73.1	11.7	6.4	2.7	2.2	0.9	**20.3**	**26.2**	**12.7**	99.9	53.8	11.5	0.6	2.0	1.1	2.6	3.1	1.3	7.0	1.6	1.7
	Cxcl13	4	15.7	6.2	3.3	**32.1**	**8.2**	**17.0**	149.6	33.2	16.5	0.8	0.5	0.1	0.7	2.8	0.3	23.8	1.1	2.0	15.2	2.2	3.4	4.7	**8.0**	**6.2**	89.2	8.3	4.7	0.1	0.5	0.3	1.8	1.2	3.4	1.8	1.1	1.4
	Ccl8	5	4.3	4.2	2.3	**8.1**	**27.1**	**48.0**	4.1	92.5	36.1	5.4	6.4	2.0	**7.9**	**16.5**	**21.4**	3.7	12.4	13.5	2.9	3.4	0.9	2.5	**12.7**	**21.0**	1.6	8.2	7.2	1.5	2.2	2.3	0.9	3.8	0.8	1.0	1.6	0.8
	Il6	6	1.7	0.9	1.4	2.8	**12.9**	**15.3**	20.5	55.6	106.5	0.4	0.5	0.5	0.8	0.9	0.5	1.8	0.6	0.7	1.9	1.6	1.2	1.3	**7.7**	4.2	5.4	9.1	2.8	0.5	1.0	0.7	0.5	0.6	0.4	0.5	0.7	0.6
	Ccl7	16	1.4	1.1	1.0	**12.0**	**12.7**	**13.8**	29.6	22.6	12.5	1.3	1.6	1.2	**6.7**	4.8	1.9	21.9	4.0	1.2	2.3	1.5	0.8	2.1	**12.1**	4.6	14.8	15.6	2.4	1.2	3.3	1.2	1.7	2.4	1.8	10.1	1.8	6.9
	Cxcl9	21	2.3	4.0	2.8	**10.4**	**25.2**	**17.4**	17.0	18.9	5.8	0.4	0.4	0.2	1.1	1.4	0.6	2.9	0.8	0.8	10.4	6.7	6.4	**19.7**	**13.3**	**8.5**	46.7	16.4	9.0	2.1	3.4	0.6	1.8	1.7	2.4	0.9	1.8	2.3
	Cxcl10	22	1.6	1.8	3.0	**17.2**	**18.8**	**11.4**	22.0	10.1	6.1	0.6	1.2	2.7	**7.6**	**6.5**	2.6	10.6	4.8	2.2	6.4	6.9	3.1	**45.1**	**42.7**	**17.5**	89.4	28.0	9.8	0.2	0.3	0.3	3.0	1.6	2.6	1.8	0.9	0.8
	Cxcl2	23	1.6	0.7	1.6	**6.3**	**8.4**	**9.4**	29.0	12.3	17.0	1.5	1.9	1.2	1.8	1.7	2.9	8.1	5.3	1.2	0.7	0.8	0.5	2.5	3.3	3.0	10.5	6.6	3.1	1.7	0.9	4.7	0.7	1.0	1.2	0.9	0.7	0.9
	Ccl19	30	1.5	1.1	1.1	**14.5**	**15.7**	**6.2**	15.4	12.9	6.8	0.4	0.3	0.4	0.8	2.3	0.4	0.5	0.8	0.3	3.4	0.9	1.5	3.7	**7.9**	2.3	3.7	3.5	1.7	0.6	0.4	1.2	0.8	1.1	1.0	0.4	0.7	0.8
Mmp	Mmp3	29	1.2	1.0	0.6	4.6	**14.2**	**10.4**	15.9	12.3	17.0	1.1	0.6	0.6	2.3	1.4	0.7	1.2	1.2	1.1	2.5	1.6	1.4	4.1	4.5	3.4	4.4	6.2	2.5	1.4	0.8	4.4	3.0	**5.3**	2.8	3.6	1.0	6.0
	Mmp12	39	8.0	3.1	2.3	**9.6**	**15.6**	**5.9**	9.8	10.2	13.3	0.7	0.4	0.5	1.0	1.8	1.8	1.2	2.0	2.1	1.2	2.6	1.6	2.0	4.6	3.2	1.0	5.2	4.8	2.2	0.6	0.6	1.7	0.7	2.0	0.5	0.9	2.0
	Mmp19	501	2.8	3.1	1.9	1.9	2.2	**5.2**	6.1	2.3	4.2	0.4	1.2	1.1	0.6	0.6	0.8	1.1	0.6	0.5	0.5	0.9	0.9	0.6	1.2	1.4	2.0	1.0	0.6	8.5	1.4	8.7	4.5	4.5	1.2	3.2	1.3	1.5
	Mmp9	516	3.3	2.3	2.6	2.4	4.3	2.8	4.9	4.7	2.7	4.0	4.2	4.9	4.9	3.5	5.4	14.5	5.6	3.0	1.0	0.5	0.9	0.7	0.5	0.7	2.1	1.1	0.8	0.3	0.3	0.9	1.0	1.2	2.0	2.6	2.1	1.2
	Mmp8	2617	0.8	1.2	0.6	1.0	1.0	0.7	7.3	1.7	1.4	0.7	0.7	0.7	0.8	0.6	1.2	5.7	1.3	0.9	1.5	0.9	0.7	0.7	1.3	2.2	21.3	2.9	0.6	0.2	0.6	0.9	0.4	0.7	0.5	0.5	0.6	0.2
	Mmp20	3942	0.7	0.9	1.5	1.0	1.5	4.4	1.0	1.8	1.7	0.5	1.2	1.2	0.6	0.7	1.1	0.7	1.0	0.6	0.6	0.7	1.0	0.5	1.1	0.8	0.5	0.7	0.6	1.9	2.7	3.0	1.4	1.7	1.2	1.4	2.4	3.9
	Mmp14	4046	1.3	1.7	1.3	1.2	1.5	2.1	2.4	1.7	2.4	1.6	2.2	1.3	1.5	0.9	1.7	1.2	1.0	2.4	1.4	2.2	2.0	1.1	1.8	2.5	1.9	2.7	2.2	2.6	1.2	2.8	0.6	1.8	0.6	1.4	1.6	1.1
	Mmp1a	4838	0.8	0.7	1.3	**5.3**	1.0	1.1	0.8	0.9	1.4	0.6	0.8	1.0	1.0	0.7	0.6	0.9	0.9	0.7	1.5	2.2	2.6	1.9	1.6	1.4	1.3	1.2	1.6	1.1	0.9	0.3	0.3	0.5	0.5	0.3	0.2	1.7
	Mmp27	6457	1.3	1.4	0.9	1.3	1.0	1.2	1.6	2.8	1.9	0.6	1.1	1.0	1.0	1.2	4.6	1.1	1.0	0.7	0.8	3.3	0.7	0.5	1.0	0.8	0.9	0.8	0.6	0.6	1.0	0.6	1.4	**7.5**	0.4	0.6	0.9	0.7
	Mmp7	6484	1.9	0.8	1.9	0.9	0.7	2.7	1.9	2.5	1.1	0.7	0.6	0.6	0.4	0.6	0.5	0.4	0.6	0.5	0.7	1.0	0.8	0.6	0.6	1.0	0.4	0.8	0.9	0.9	0.7	0.7	0.7	0.9	0.8	0.6	1.1	0.9
Cam	Vcam1	40	2.5	1.3	0.9	**15.1**	**9.9**	**6.2**	14.8	10.6	5.7	2.4	1.4	3.3	**23.4**	**5.4**	**6.1**	12.3	11.2	10.0	1.6	1.4	1.0	**18.7**	**6.2**	3.6	12.0	15.1	4.1	0.1	0.4	1.1	1.0	1.5	0.8	1.4	0.9	0.6
	Icam1	258	1.7	1.4	1.1	**5.0**	4.1	3.5	10.1	3.4	2.0	1.4	1.3	2.1	4.8	2.7	3.0	6.0	4.1	2.7	1.4	1.0	1.0	3.3	2.8	2.4	6.2	2.7	1.2	0.4	0.7	1.0	1.3	2.0	2.1	2.4	1.5	1.1
	Selp	311	1.8	1.2	0.7	3.3	3.4	3.7	10.0	2.9	2.6	3.9	1.7	3.3	**5.1**	1.0	2.5	4.9	4.7	23.9	10.4	5.4	8.1	**13.1**	**15.0**	**14.9**	27.4	18.1	13.7	3.4	1.2	6.9	0.9	0.9	0.9	1.1	1.4	2.2
	Madcam1	401	2.0	1.5	1.4	4.6	**5.6**	2.0	7.2	2.6	1.7	1.1	1.0	0.6	1.5	3.0	1.2	2.8	1.0	1.0	2.2	0.8	0.5	2.5	2.7	1.7	5.4	2.2	2.0	0.6	0.6	1.6	0.8	1.6	1.4	0.6	1.4	1.6
	Jam2	2360	1.3	1.3	1.5	2.0	1.1	1.8	1.1	6.2	1.1	2.4	1.2	1.0	0.7	0.4	1.7	3.3	0.5	2.4	1.3	4.5	2.1	1.9	1.5	1.3	1.3	1.4	2.0	1.7	1.1	1.7	1.0	1.3	2.3	1.8	1.1	6.6
	Cd34	3999	1.6	1.6	1.3	1.0	2.1	2.5	2.2	0.9	2.7	1.7	1.1	0.5	1.1	0.9	1.4	1.5	1.6	3.3	1.0	0.9	1.1	0.8	0.9	0.7	1.1	0.5	0.7	1.2	1.8	1.2	0.7	1.7	1.0	1.3	1.6	0.8
	Jam3	7317	1.2	3.5	4.2	1.3	1.8	2.4	1.4	1.3	1.4	1.3	0.6	0.8	1.0	1.2	0.9	1.3	1.6	1.2	1.9	3.2	1.7	1.9	1.0	0.9	1.4	2.0	1.7	3.6	2.3	0.6	0.9	0.5	1.4	0.5	0.7	0.9
	Sele	12984	1.0	0.9	0.9	1.1	1.1	1.2	2.2	1.2	1.0	0.7	0.7	0.5	1.8	0.7	0.9	1.4	0.9	1.1	1.2	1.0	1.8	2.9	1.7	2.6	9.9	2.3	1.2	0.9	2.0	3.1	0.8	1.5	0.7	0.8	0.9	1.4
	Pvrl2	13254	2.2	0.8	1.2	2.9	1.3	1.4	0.8	0.5	0.7	1.4	0.8	1.0	1.2	1.6	1.3	1.3	0.8	1.1	0.9	0.9	1.3	0.6	1.5	1.4	0.9	1.2	1.3	0.5	0.7	0.7	0.3	0.8	0.4	0.5	0.4	1.7
	Icam2	15175	1.0	1.0	1.2	1.1	1.5	1.4	1.3	0.8	1.3	1.3	1.0	1.5	1.1	1.0	1.3	1.0	1.8	2.3	1.3	0.9	1.3	1.9	1.1	1.3	1.3	0.6	1.2	0.6	1.3	0.6	1.7	1.5	4.3	3.6	0.9	1.6

Top 10 genes in the all, Chemokine/cytokine, Mmp and Cell adhesion molecule (Cam) categories are listed among the genes of which expression levels were enhanced in aortic root after oral administration of FK565 with or without LPS priming at days 2, 4 and 7, compared with those without administration. We prepared each 10 mice in the same condition, 7 of which were used for in vivo microarray analysis and the remaining 3 were sacrificed for the histopathology study of heart. At day 2, the sections showed mild cellular infiltration in aortic valve. At day5, the cellular infiltration with edema was enhanced in aortic valve. Then, at day7, marked coronary arteritis and valvulitis were observed. Numbers in rank refer to the order of the gene expression levels in all categories. Data are expressed as fold changes of the respective gene expression levels after stimulation. Numbers in bold in FK565-stimulated vascular tissues and spleen refer to those over 5-fold increases. The genes in the category "Chemokine/cytokine" were selected from those listed in Cytokine- cytokine receptor interaction (map04060), and the genes in the category "Cam" were from those listed in the Endothelial cell, Leukocyte transendothelial migration in Cell adhesion molecules (map04514) in the KEGG database (http://www.genome.jp/kegg/pathway.html). Gene full names are as follows. Ccl5, chemokine (C-C motif) ligand 5; Arg1, arginase, liver; Ccl2, chemokine (C-C motif) ligand 2; Cxcl13, chemokine (C-X-C motif) ligand 13; Ccl8, chemokine (C-C motif) ligand 8; Il6, interleukin 6; Serpina3n, serine (or cysteine) peptidase inhibitor, clade A, member 3N; Saa3, serum amyloid A 3; Cfb, complement factor B; Lcn2, lipocalin 2; Ccl7, chemokine (C-C motif) ligand 7; Cxcl9, chemokine (C-X-C motif) ligand 9; Cxcl10, chemokine (C-X-C motif) ligand 10; Cxcl2, chemokine (C-X-C motif) ligand 2; Cxcl19, chemokine (C-X-C motif) ligand 19; Mmp, matrix metallopeptidase; Vcam1, vascular cell adhesion molecule 1; Icam1, intercellular adhesion molecule 1; Selp, selectin, platelet; Madcam1, mucosal vascular addressin cell adhesion molecule 1 ; Jam2, junction adhesion molecule 2; Cd34, CD 34 antigen; Jam3, junction adhesion molecule 3; Sele, selectin, endothelial cell; Pvrl2, poliovirus receptor-related 2; Icam2, intercellular adhesion molecule 2. When 2 or more genes were picked up by different probes, only one with the highest rank is included in the list (Rank 8 is Il6). Microarray analysis data are shown in Fig. 4Ab.

Supplementary Table III. Top 10 genes expressed in aortic root *ex vivo* and HCAEC *in vitro* stimulated with FK565.

A

Category	Gene Symbol	Rank	AR	PA	Aorta
All	Gm4022	1	28.3	0.7	1
	Gm3727	2	26.7	1.2	1.1
	Ccl5	3	25.8	32.7	22.3
	Krt42	4	20.3	0.8	0.6
	Gm7225	5	20.2	1.0	1.0
	Gm4477	6	18.7	1.3	0.9
	Prlr	7	17.9	2.1	1.0
	Gm15761	8	17.3	1.0	4.8
	Gm7732	9	16.7	1.1	1.0
	Gm7877	10	16.5	0.4	0.6
Chemokine/ cytokine	Ccl5	3	25.8	32.7	22.3
	Ccl22	45	11.0	1.0	0.7
	Kitl	86	9.3	1.9	1.2
	Osm	113	8.7	3.6	0.9
	Il1b	392	5.6	0.9	0.7
	Il6	417	5.5	1.9	1.5
	Cxcl10	638	4.7	0.8	0.4
	Ccl2	880	4.1	4.5	2.1
	Il12b	1227	3.6	3.1	0.7
	Cxcl16	1451	3.3	2.2	4.6
Mmp	Mmp3	1322	3.5	2.2	2.0
	Mmp27	5397	1.9	1.6	5.0
	Mmp7	5453	1.9	1.0	2.6
	Mmp12	7387	1.6	2.0	1.2
	Mmp10	8276	1.5	0.7	0.9
	Mmp19	10649	1.4	0.4	2.0
	Mmp15	12572	1.3	0.7	2.5
	Mmp11	13380	1.3	2.1	0.6
	Mmp24	17089	1.1	1.2	0.9
	Mmp20	17299	1.1	1.2	1.4
Cam	Vcam1	1331	3.5	6.1	8.7
	Pecam1	2742	2.5	0.7	1.5
	Icam1	3917	2.2	3.1	2.6
	Selp	6266	1.8	3.3	1.5
	F11r	8175	1.6	1.4	1.2
	Pvrl2	10882	1.4	0.7	0.4
	Jam3	10972	1.4	0.6	1.2
	Jam2	13969	1.2	1.3	1.2
	Icam2	15417	1.2	1.8	1.0
	Cd34	16883	1.1	1.8	1.9

B

Category	Gene Symbol	Rank	HCAEC		HPAEC	
			FK565	Lipid A	FK565	Lipid A
All	UBD	1	70.3	6.4	43.9	0.7
	PRMT8	3	31.5	1.8	1.1	0.5
	PRRX1	4	20.8	2.4	0.2	0.5
	SH3GL2	5	14.3	1.0	0.8	1.6
	CES1	6	14.3	0.9	1.4	2.3
	PRM1	7	13.2	2.3	1.0	0.9
	C1orf81	8	12.3	1.0	0.7	1.3
	CCL2	9	10.5	3.1	5.3	2.9
	PAMR1	10	10.5	0.8	0.5	0.6
	GNPTAB	11	9.6	2.8	2.2	1.0
Chemokine/ cytokine	CCL2	9	10.5	3.1	5.3	2.9
	CCL5	41	6.0	6.3	4.5	2.9
	CSF2	43	5.8	2.1	0.8	3.9
	LTB	58	5.4	0.8	6.8	1.9
	IL29	124	4.2	1.3	0.3	0.3
	IL5	252	3.3	1.7	8.0	1.5
	CCL20	427	2.9	2.0	1.4	1.6
	CXCL3	446	2.9	2.7	1.5	1.2
	IL6ST	453	2.9	1.8	1.7	0.5
	CXCL9	476	2.9	1.0	1.2	1.0
MMP	MMP9	30	6.7	1.1	0.9	1.5
	MMP3	600	2.7	2.5	1.5	0.8
	MMP10	1675	2.0	1.6	2.4	1.6
	MMP13	1862	2.0	1.9	2.8	0.6
	MMP28	2800	1.8	1.2	0.7	1.1
	MMP23B	4671	1.5	1.1	0.8	0.9
	MMP25	5844	1.5	0.5	1.8	1.5
	MMP12	7211	1.4	1.2	2.5	1.3
	MMP16	7467	1.4	0.8	1.0	1.2
	MMP27	11675	1.2	1.6	1.2	1.1
CAM	ICAM1	53	5.6	2.0	4.4	1.5
	MADCAM1	921	2.4	1.2	1.0	1.4
	VCAM1	1323	2.2	2.0	0.9	1.2
	CD34	1996	2.0	1.8	1.7	3.6
	CD58	4737	1.5	1.3	1.0	0.8
	F11R	12407	1.2	0.9	1.0	0.6
	JAM3	20960	1.0	1.2	0.9	1.2
	ICAM3	24950	1.0	1.0	1.0	1.0
	ICAM2	25062	1.0	0.9	1.0	1.0
	JAM2	27109	0.9	0.9	1.3	0.8

A. Top 10 genes in the all, Chemokine/cytokine, Mmp and Cam categories are listed among the genes of which expression levels were enhanced in aortic root *ex vivo* cultured for 24 hours with FK565 (10μg/mL) compared with those without stimulation by microarray analysis. Numbers in rank refer to the order of the gene expression levels in all categories. Data are expressed as fold changes of the respective gene expression levels after FK565 stimulation. Selection of the genes in each category is described in SupplementaryTable II. Gene full names are as follows. Gm4022, predicted gene 4022; Gm3727, predicted gene 3727; Krt42, keratin 42; Gm7225, predicted gene 7225; Gm4477, predicted gene 4477; Prlr, prolactin receptor; Gm15761, predicted gene 15761; Gm7732, predicted gene 7732; Gm7877, predicted gene 7877; Ccl22, chemokine (C-C motif) ligand 22; Kitl, kit ligand; Osm, oncostatin m; Il1b, interleukin 1 beta; Il12b, interleukin 12b; Cxcl16, chemokine (C-X-C motif) ligand 16; Pecam1, platelet/endothelial cell adhesion molecule 1; F11r, F11 receptor; When 2 or more genes were picked up by different probes, only one with the highest rank is included in the list. AR: aortic root, PA: pulmonary artery, Aorta: arch portion of aorta. Microarray analysis data are shown in Supplementary Fig. IVA.

B. Top 10 genes in the all, Chemokine/cytokine, human matrix metallopeptidase (MMP) and human cell adhesion molecule (CAM) categories are listed among genes of which expression levels were enhanced in HCAEC after 24 hours stimulation with FK565 (10μg/mL) *in vitro* compared with those without any reagent by microarray analysis. Numbers in rank refer to the order of the gene expression levels in all categories. Data are expressed as fold changes of the respective gene expression levels after stimulation. Selection of the genes in each category is described in Supplementary Table II. Gene full names are as follows. UBD, ubiquitin D; PRMT8, protein arginine methyltransferase 8; PRRX1, paired related homeobox 1; SH3GL2, SH3-domain GRB2-like 2; CES1, carboxylesterase 1 (monocyte/macrophage serine esterase 1); PRM1, protamine 1; C1orf81, hypothetical protein LOC647215; CCL2, chemokine (C-C motif) ligand 2; PAMR1, regeneration associated muscle protease; GNPTAB, N-acetylglucosamine-1-phosphate transferase, alpha and beta subunits; CCL5, chemokine (C-C motif) ligand 5; CSF2, colony stimulating factor 2 (granulocyte-macrophage); LTB, lymphotoxin beta (TNF superfamily, member 3); IL29, interleukin 29 (interferon, lambda 1); IL5, interleukin 5 (colony-stimulating factor, eosinophil); CCL20, chemokine (C-C motif) ligand 20; CXCL3, chemokine (C-X-C motif) ligand 3; IL6ST, interleukin 6 signal transducer (gp130, oncostatin M receptor); CXCL9, chemokine (C-X-C motif) ligand 9; ICAM1, intercellular adhesion molecule 1; MADCAM1, mucosal vascular addressin cell adhesion molecule 1; VCAM1, vascular cell adhesion molecule 1; CD34, CD34 molecule ; CD58, CD58 molecule; F11R, F11 receptor; JAM3, junction adhesion molecule 3; ICAM3, intercellular adhesion molecule 3; ICAM2, intercellular adhesion molecule 2; JAM2, junction adhesion molecule 2. When 2 or more genes were picked up by different probes, only one with the highest rank is included in the list (Rank 2 is UBD). Microarray analysis data are shown in Supplementary Fig. IVB.

Supplemental Material.

METHODS

Ligands. γ-D-glutamyl-*meso*-diaminopimelic acid (iE-DAP) was synthesized by Fujimoto Y. and Fukase K. FK565 and FK156 were supplied by Astellas Pharmaceutical. OK-432 (Picibanil), a viable but static *Streptococcus pyogenes* after penicillin-treatment, was supplied by Chugai Pharmaceutical. LPS from *Escherichia coli* O111:B4 (a ligand for TLR4 and other receptors), and zymosan (a ligand for TLR2 and dectin 1)[1] were purchased from Sigma. *E. coli*-type synthetic LPS lipid A (a ligand for TLR4) was purchased from Peptide Institute. *E.coli*-type synthetic lipid A is the lipid portion of bacterial LPS, the bioactive center of LPS toxicity[2]. Peptidoglycan from *E.coli K12* (PGN K12), and synthetic MDP (a ligand for NOD2) were purchased from InvivoGen. Synthetic NOD ligands (iE-DAP, FK565, FK156, and MDP) showed no endotoxin contamination (less than 0.05 EU/mL by Toxinometer ET-5000, Wako).

Cell stimulation experiments. HCAEC and HPAEC were cultured in EBM-2 medium with EGM-2MV and EGM-2 (Lonza), respectively, in a CO_2 (5%) incubator at 37°C[3]. These cells, between passages 6 and 10, were suspended and seeded into 6- or 12-well plates (3-5 day culture: 1×10^4 cells/well and 1 day culture: 1, 1.6 or 4×10^4 cells/well). One day later, the medium was changed and cells were stimulated with each

reagent or combined reagents at various concentrations for 1, 3 or 5 days. We performed these experiments four times independently.

Flow cytometric analyses. Cells were stained with fluorescein isothiocyanate (FITC)-conjugated anti-CD54 mAb (Beckman Coulter). The expression levels of ICAM-1 were analyzed by an EPICS XL flow cytometer (Beckman Coulter)[4,5]. Culture supernatants were harvested and the concentrations of IL-8, IL-6, IL-1β, TNF-α, IL-12p70, Interferon (IFN) γ, IL-10 and CCL2 were measured by BD™ Cytometric Bead Array human and mouse inflammation kits and human chemokine kit (BD Biosciences).

RNA interference (RNAi). HCAEC (4 x 10^4 cells/well) were transfected by NOD1 Stealth RNAi small interfering RNA (siRNA) (HSS115906 or HSS115908, Invitrogen) and Stealth RNAi siRNA Negative Control Med GC (Invitrogen) using Lipofectamin RNAiMAX (Invitrogen) for knockdown of endogenous NOD1 and negative control, respectively. Thirty pmol siRNA per well was used for transfection with Lipofectamin RNAiMAX according to manufacturer's recommendation (Invitrogen) and preliminary experiments. The viability of the cells was over 95% without morphological change at day 1. After transfection for 22hr, HCAEC were stimulated by each reagent or combined reagents for 1 day. We performed these experiments twice independently.

Animal experiments. BALB/c, C57BL/6, DBA/2, CD-1, CBA/J, C3H and SCID

(C57BL/6 background) mice were purchased from KBT Oriental, Charles River Grade. Nod1 $^{-/-}$ mice in C57BL/6 background were a gift from Tak Mak, University Health Network. All mice were 5- to 9-week-old female, and were housed in a specific pathogen-free environment. Experiments were performed three times independently under barrier conditions at the animal facility of the biosafety level P1A. These animal experiments were performed according to the protocol approved by the Kyushu University Institutional Animal Care and Use Committee.

Immunohistochemistry. All sections for immunohistochemistry were 4% paraformaldehyde-fixed and paraffin-embedded. Primary antibodies used were Nod1-specific antibody (1:1000, IMGENEX)[6], F4/80 (macrophage)-specific antibody (1:100, Abcam), NIMP-R14 (neutrophil)-specific antibody (1:1500, Abcam), CD3 (T cell) -specific antibody, (1:400, Abcam), alpha smooth muscle actin-specific antibody (1:100, Dako), and CD31-specific antibody (Platelet endothelial cell adhesion molecule 1) (1:50, Abcam) used for the detection of endothelial cells. Deparaffinized sections with or without antigen retrieval (citrate buffer pH6.0 or trypsin) were incubated with 3% nonfat milk to eliminate nonspecific binding and with peroxidase-labeled secondary antibody (Dako and Nichirei) following the primary antibodies. Horseradish peroxidase activity was visualized with Peroxidase Stain DAB Kit (Nacalai Tesque) to give the reaction

product a brown color, and then the sections were counterstained with hematoxylin.

Quantitative real-time RT-PCR. Total RNA was extracted from HCAEC and murine tissues using RNeasy Micro kit and RNeasy Fibrous Tissue (Qiagen), respectively, followed by cDNA synthesis using a High Capacity RNA-to-cDNA kit (Applied Biosystems). Human NOD1 and mouse Nod1 mRNA expression levels were analyzed by TaqMan® Gene Expression Assay Hs00196075_m1 and Mm00805062_m1 (Applied Biosystems), respectively, and TaqMan Gene Expression Master Mix (Applied Biosystems). Human GAPDH (Pre-Developed TaqMan Asssay Reagents GAPDH Control Reagents, Applied Biosystems), mouse GAPDH (primers: CCTGGAGAAACCTGCCAAGTAT, TTGAAGTCGCAGGAGACAACCT; TaqMan probe: VIC-TGCCTGCTTCACCACCTTCTTGATGT-TAMRA) and Cadherin 5 (CDH5, Mm00486938_m1, Applied Biosystems) were used as internal controls. Calibration curve was generated with serial 5-fold dilutions. The mRNA expression levels of the targeted genes were quantified by an ABI PRISM 7700 or Applied Biosystems StepOnePlus sequence detector (Applied Biosystems), as described[4].

Organ Culture. Each tissue of aortic root, pulmonary artery, aortic arch, and abdominal aorta (between roots of right and left renal arteries) sterilely isolated from BALB/c or $Nod1^{-/-}$ mice was cultured for 24 hours in a 96-well plate with EBM-2 medium and

EGM-2 (Lonza) in the presence or absence of an indicated reagent in a CO_2 (5%) incubator at 37°C. We performed these experiments four times independently.

Protein determination. Protein concentrations of each tissue were measured by Bio-Rad protein assay (BioRad) after homogenization with phosphate buffered saline containing Cell Culture Lysis Reagent (Promega) and Protease Inhibitor Cocktail (Nacalai Tesque). Whole protein contents of each tissue were measured to calculate CCL2/IL-6 levels per tissue protein contents.

Microarray analysis. Microarray analysis was performed with *in vivo*-treated and *ex vivo*-cultured organs isolated from 7 mice and *in vitro*-cultured cells (1 x 10^4 cells). Total RNA was extracted from murine tissues with an RNeasy Fibrous Tissue and from human cell lines with RNeasy Micro Kit (Qiagen). Total RNA was then amplified using Amino Allyl MessageAmp™ II aRNA Amplification Kit (Ambion). Briefly, double-standard complementary DNA (cDNA) was synthesized from total RNA and *in vitro* transcription was performed to produce multiple copies of amino allyl-labelled complementary RNA (cRNA). Amino allyl-labelled cRNA was purified, reacted with N-hydroxy succinimide esters of Cy3 (GE Healthcare) using Nimblegen's protocol and hybridized for 19h at 42°C to the mouse and human Nimblegen Gene Expression arrays (090901_MM9_EXP_HX12, and 090828_HG18_opt_expr_HX12, Roche NimbleGen)

that contain approximately 40,000 genes. The arrays were scanned on Gene Pix 4000B (Molecular Devices Corporation). The averages of triplicate spot intensity data were extracted using NimbleScan v2.5 (Roche NimbleGen) and processed using robust multiarray analysis method[7]. The scaled gene expression values were imported into GeneSpring 11.0 software (Agilent Technologies) for preprocessing and data analysis[4]. The expression value of each gene was normalized to the 75 percentile shift expression of all genes in each chip. Probe sets were deleted from subsequent analysis if they were displayed an absolute value below 30 in all experiments. The normalized data were first $\log_2$ transformed. For each gene, $\log_2$ intensities from stimulated samples were compared by non-stimulated samples. Microarray data were deposited in Gene Expression Omnibus under accession numbers, GSE20929 (*in vitro* gene expression) and GSE20930 (*in vivo* and *ex vivo* gene expression). Microarray experiments of in vivo organs from 7 mice were done once but on 3 different days 2, 4 and 7 after treatment with consistent results.

Statistical Analysis. Data were analyzed by Student's t-test, Dunnett's test or Tukey-Kramer honestly significant difference (HSD) test using a statistical software, JMP version 8.0 (SAS Institute).

Supplementary Figure I: Primary augmenting effects between NOD1 and TLR ligands in HCAEC

A. Effects of innate immune stimulants on HCAEC at day 1.

HCAEC (1 x 10^4 cells for ICAM-expression; 1.6 x 10^4 cells for cytokine production) were incubated with NOD1, NOD2, TLR and other stimulants in various combinations for 24 h. ICAM-1 expression (a) and IL-8 (b) /IL-6 (c) production in the culture supernatants were investigated in triplicate at day 1. The concentrations of stimulants are as follows: iE-DAP, MDP and PGN K12, 1 (▒) or 10 (■) μg/mL; lipid A 10 (▒) or 100 (■) ng/mL. Data are presented as mean ± s.d. *: $P < 0.01$ compared with medium, †: $P < 0.01$ compared with either iE-DAP or Lipid A, ‡: $P < 0.01$ compared with either PGN K12 or Lipid A (Dunnett's test).

B. NOD1 knockdown suppresses the stimulatory effects of NOD1 ligand in the absence or presence of TLR4 ligand in HCAEC.

HCAEC (4 x 10^4 cells) were transfected with either siRNA against NOD1 (#1: HSS115908 or #2: HSS115906) or a non-targeted control siRNA. NOD1 siRNA (#1) and (#2) reduced the expression levels of endogenous NOD1 in HCAEC to 15.9 ± 1.9% and 37.0 ± 7.5% of those treated with control siRNA, respectively, as confirmed by quantitative RT-PCR (data not shown). Secretion levels of IL-8 (a) and IL-6 (b) were

investigated in triplicate at 24 hr after stimulation. The concentrations of stimulants are as follows: iE-DAP and MDP, 10 μg/mL; lipid A 100 ng/mL. Data are presented as mean ± s.d. The effects of NOD1 ligand, iE-DAP, were almost completely inhibited, while those of TLR4 ligand (LipidA) remained uninhibited by NOD1 siRNA (#1). *: $P < 0.01$ compared with those treated with a control siRNA. The additive effect of NOD1 and TLR4 was abolished after NOD1 siRNA (#1) treatment. †: $P < 0.01$ compared with either iE-DAP or Lipid A (Dunnett's test).

Supplementary Figure II. Chemical structures of NOD1 ligands and comparison of the effects on HCAEC.

A. Chemical structures of diaminopimelic acid (DAP)–type peptidoglycan and synthetic NOD1 ligands. iE-DAP: γ-D-Glu-DAP, a synthetic dipeptide with a molecular weight (M.W.) of 319.3 daltons, FK565: heptanolyl-γ-Glu-*meso*-DAP-D-Ala, a synthetic acyltripeptide with a M.W. of 502.6 daltons, FK156: D-lactyl-L-Ala-γ-Glu-*meso*- DAP-Gly, with a M.W. of 519.5 daltons, a synthetic tetrapeptide, originally isolated from culture filtrates of *Streptomyces* strains.

B. HCAEC (4×10^4 cells) were incubated with one of Nod1 stimulants, FK565, FK156 or iE-DAP. ICAM-1 expression (a) and CCL2 (b) /IL-8 (c) production in the culture

supernatants were examined at day 3. The concentrations are 1 (▒) or 10 (■) μg/mL. Data are presented as mean ± s.d. (N=4). *: P <0.01, vs medium; †: P < 0.01, vs. FK 156; ‡: P < 0.01, vs. iE-DAP (Dunnett's test).

Supplementary Figure III. Immunohistochemial studies of coronary arteritis induced by oral administration of FK565.

All the sections were serial ones of aortic root from coronary arteritis model which was orally administrated by FK565 100μg for 6 consecutive days after priming of LPS 20μg i.p. Inflammatory cells infiltrating in the both coronary and aorta including valve consisted of many NIMP-R14-positive neutrophils, some F4/80-positive macrophages, and few CD3-T lymophocytes. Endothelial cells, smooth muscle cells and fibroblasts/myofibroblasts in addition to infiltrating inflammatory cells were apparently positive for NOD1. H&E stain (W: aortic root, x 40 (A: aortic valve (AV), B: coronary artery (CA)); A1: AV, x 400; B1: CA, x 400) and immunohistochemical stainings with Nod1- (A2: AV, B2: CA, x400), F4/80 (macrophage)- (A3: AV, B3: CA, x400), NIMP-R14 (neutrophil)- (A4: AV; B4: CA, x 400), CD3- (A5: AV; B5: CA, x 400), CD31- (B6: CA, x 400), and alpha smooth muscle actin- (B7: CA, x 400) specific antibodies.