Suppl. Table S1. Characterization of Ag nanoparticles.

	Time point (h)	Approx. size peak max (nm)	Scattered light intensity (average, kcps)	Zeta-potential (average, mV)
Ag10	0 h	10, 1000	730	-0.587
	24 h	10, 100, 1000	63	N.D.
Ag75	0 h	3.5, 40, 400	2790	-7.78
	24 h	5, 100, 1000	1100	N.D.

Ag nanoparticles (primary particle size: 10 nm and 75 nm) were dispersed in bronchial epithelial growth medium (BEGM) and hydrodynamic size distribution and zeta potential values were determined. The data are reproduced from Gliga et al. Sci. Reports. 2018 (8):6668 [Creative Commons licence].

Suppl. Table S2. Canonical pathways enriched after long-term exposure of BEAS-2B cells to Ag nanoparticles.

Ingenuity Canonical Pathways	p-value	z-score	n	Gene symbols
Leukocyte Extravasation Signaling	0.001	0.39	28	*TIMP3, FGFR2, FGFR3, CXCR4, VAV3, ITGA1, F11R, EDIL3, MAP3K4, FER, PIK3C3, PIK3R3, MAPK14, AFDN*, *TIMP4, ITGA5, TEC, WIPF1, CLDN15, MMP19, THY1, MMP11, ITGB2, JAM2, FGFR4, CYBA, ITGA4, MMP2*
Dendritic Cell Maturation	0.002	0.20	26	*FGFR2, FGFR3, HLA-DQB1, IL1A, IL1B, IL18, MYD88, PIK3C3, CREB1, PIK3R3, ATF2, MAPK14,* *CD83, PLCE1, PLCH1, COL1A1, HLA-DMA, PLCL2, PLCD4, LY75, CREB5, FGFR4, COL18A1, TNFRSF1B, COL1A2, DDR2*
Acute Phase Response Signaling	0.002	-0.94	24	*FGG, IL1A, IL1B, SAA2, FGA, IL18, SOCS2, MAP3K5, MAP3K1, IL6ST, MYD88, SOD2, SOCS5, PIK3R3, SOCS6, MAPK14*, *FTL, RBP7, RBP1, CRABP2, ITIH3, TNFRSF1B, MRAS, SERPINF1*
Inflammasome pathway	0.002	-0.82	6	*IL1B, IL18, NEK7, MYD88,* *NLRP1, P2RX7*
Clathrin-mediated Endocytosis Signaling	0.004	NA	26	*FGFR2, ITGB6, FGFR3, AP1M2, PDGFC, PIK3C3, DNM1L, PIK3R3, USP9X*, *ITGA5, LDLRAP1, PDGFB, CLU, DAB2, EPHB2, DNM1, APOC1, ITGB2, F2R, FGFR4, PGF, DNM3, SH3KBP1, SNAP91, ARRB1, APOD*
IL-8 Signaling	0.011	0.63	24	*CCND2, FGFR2, FGFR3, CDH1, ANGPT1, RND3, EGFR, PDGFC, PIK3C3, PIK3R3, MAP4K4*, *BCL2, KDR, GNG11, GNB3, MYL9, ITGB2, FGFR4, PGF, GNG2, MRAS, IRAK2, GNG7, MMP2*
p38 MAPK Signaling	0.012	-0.54	16	*IL1A, IL1B, IL18, MAP3K5, TGFBR1, CREB1, ATF2, MAPK14*, *FADD, RPS6KA2, TGFB1, DDIT3, MEF2C, CREB5, TNFRSF1B, IRAK2*
IL-7 Signaling Pathway	0.013	0.58	13	*FGFR2, FGFR3, PIK3C3, CDKN1B, PIK3R3, MAPK14*, *STAT5B, BCL2, FOXO6, IL7, FYN, FGFR4, EBF1*
FLT3 Signaling in Hematopoietic Progenitor Cells	0.034	-0.58	12	*FGFR2, FGFR3, PIK3C3, CREB1, PIK3R3, ATF2, MAPK14*, *STAT5B, RPS6KA2, CREB5, FGFR4, MRAS*
IL-9 Signaling	0.039	-0.82	7	*FGFR2, FGFR3, SOCS2, PIK3C3, PIK3R3*, *STAT5B, FGFR4*
Th2 Pathway	0.041	-1.39	17	*FGFR2, FGFR3, CXCR4, HLA-DQB1, JAG2, TGFBR1, PIK3C3, PIK3R3*, *STAT5B, ACVR2A, TGFB1, HLA-DMA, ITGB2, S1PR1, FGFR4, HLA-DPB1, NOTCH3*
Role of IL-17F in Allergic Inflammatory Airway Diseases	0.044	0.00	7	*IL1B, CREB1, ATF2*, *IL17RA, RPS6KA2, CREB5, CXCL6*
Macropinocytosis Signaling	0.047	-0.38	11	*FGFR2, ITGB6, FGFR3, PDGFC, PIK3C3, PIK3R3*, *ITGA5, PDGFB, ITGB2, FGFR4, MRAS*
NF-κB Signaling	0.048	-1.34	20	*FGFR2, FGFR3, IL1A, IL1B, IL18, EGFR, MAP3K1, MYD88, AZI2, TGFBR1, PIK3C3, PIK3R3, MAP4K4*, *FADD, KDR, TNFRSF11A, FGFR4, TNFRSF1B, MRAS, GHR*
Phagosome Formation	0.049	NA	15	*FGFR2, FGFR3, RND3, PIK3C3, PIK3R3*, *ITGA5, PLCE1, PLA2R1, PLCH1, PLCL2, ITGB2, MRC2, PLCD4, FGFR4, ITGA4*

Pathway analysis was performed using Ingenuity Pathway Analysis software on the differentially expressed genes following repeated exposure of BEAS-2B cells to 1 μg/mL Ag nanoparticles (10 nm) for 6 weeks. Significantly enriched canonical pathways (p-value<0.05) filtered for relevance for immune function (i.e., cytokine signaling and cellular immune response categories) are illustrated. Some pathways are additionally characterized by z-score, a measure of the activation state of the pathway. NA, activity pattern not available. Color coding indicates direction of gene expression change: red - upregulation, blue - downregulation as compared to untreated cells.

Suppl. Table S3. Gene ontologies enriched after long-term exposure of BEAS-2B cells to Ag nanoparticles.

Biological process	p-value	Level	n	Gene symbols
TRIF-dependent toll-like receptor signaling pathway	0.002	13	10	*MAPK14,DUSP4, BIRC3, CREB1, PPP2R5D, ATF2,* *FAD, IRAK2, MEF2C, RPS6KA2*
toll-like receptor 4 signaling pathway	<0.001	12	16	*S100A14,MYD88, MAP3K1, MAPK14, DUSP4, BIRC3,CREB1, PPP2R5D, ATF2,* *FADD, PELI2, IRAK2, PIK3AP1, MEF2C, ITGB2, RPS6KA2*
toll-like receptor 9 signaling pathway	<0.001	12	13	*MYD88, MAP3K1, MAPK14,PIK3C3, DUSP4, CREB1,PPP2R5D,ATF2* *PELI2, IRAK2, PIK3AP1, MEF2C, RPS6KA2*
toll-like receptor 2 signaling pathway	<0.001	12	12	*MYD88, MAP3K1,MAPK14, DUSP4, CREB1, PPP2R5D,* *PELI2, IRAK2, PIK3AP1, MEF2C, RPS6KA2*
toll-like receptor 10 signaling pathway	<0.001	12	11	*MYD88, MAP3K1, MAPK14,DUSP4, CREB1, PPP2R5D, ATF2* *PELI2, IRAK2, MEF2C, RPS6KA2*
toll-like receptor 5 signaling pathway	<0.001	12	11	*MYD88, MAP3K1, MAPK14,DUSP4, CREB1, PPP2R5D, ATF2* *PELI2, IRAK2, MEF2C, RPS6KA2*
toll-like receptor TLR1:TLR2 signaling pathway	<0.001	12	11	*MYD88, MAP3K1, MAPK14, DUSP4, CREB1, PPP2R5D, ATF2* *PELI2, IRAK2, MEF2C, RPS6KA2*
toll-like receptor TLR6:TLR2 signaling pathway	<0.001	12	11	*MYD88, MAP3K1, MAPK14, DUSP4, CREB1, PPP2R5D, ATF2* *PELI2, IRAK2, MEF2C, RPS6KA2*
toll-like receptor 3 signaling pathway	0.002	12	10	*MAPK14, DUSP4, BIRC3, CREB1, PPP2R5D, ATF2,* *FADD, IRAK2, MEF2C, RPS6KA2*
positive regulation of GTPase activity	0.003	12	19	*EPHA1, SFRP1, RASAL2, RGS7, VAV3, SIPA1L1, ARHGEF5, ARHGAP26, EZH2, RALGAPB* *RGS2, ARRB1, RGS3, CHN2 , AXIN2, SEMA4D, THY1, S1PR1, LRRK2*
MyD88-dependent toll-like receptor signaling pathway	0.003	12	11	*MYD88, MAP3K1, MAPK14, DUSP4, CREB1, PPP2R5D, ATF2* *PELI2, IRAK2, MEF2C, RPS6KA2,*
activation of MAPKK activity	0.007	12	8	*EGFR, MAP3K5, MAP3K4, MAP3K1, TGFBR1* *F2R, TNIK, LRRK2,*
positive regulation of protein serine/threonine kinase activity	<0.001	11	29	*CCND2, EGFR, CXCR4, MAP3K5, ITGA1, CHI3L1, MAP3K4, IL1B, MAPK14, EZH2, HSP90AB1, PDCD10, THBS1, FPR1, SIRT1* *SNCA, ZEB2,DAB2, GHR, IRAK2, RGCC, CSPG4, P2RX7, PLCE1, TNFRSF11A, TGFB1, PDGFB, LRRK2, HSPA2*
regulation of MAP kinase activity	<0.001	11	30	*CAV1, EGFR, SFRP1, CXCR4, MAP3K5, ITGA1, MAP3K4, IL1B, MAPK14, EZH2, DUSP9, DUSP4, PDCD10, THBS1, FPR1* *RGS2, ZEB2, UCHL1, RGS3, DAB2, GHR, IRAK2, CSPG4, P2RX7, PLCE1, TNFRSF11A, TGFB1, PDGFB, LRRK2,SPRY1*
regulation of ventricular cardiac muscle cell action potential	<0.001	11	5	*DSP* *SCN5A, ANK2, DSC2, SCN3B*

Gene ontology analysis was performed using GOEast online tool on the differentially expressed genes following repeated exposure of BEAS-2B cells to 1 µg/mL Ag nanoparticles (10 nm) over 6 weeks. Top 15 enriched ontologies part of the biological process domain ordered according to the hierarchical level are illustrated. Color coding indicates direction of gene expression change: red - upregulation, blue - downregulation as compared to untreated cells. Level stands for hierarchical level in the gene ontology tree; the ontologies that are furthest down in the ontology tree have higher levels and increased specificity.