COPD 2016 conference
07/11/2016 13:35 - 14:20
Brisbane, Australia

The Role of Extracellular Vesicles in COPD

Tsukasa Kadota [1,2], Yu Fujita[1,2], Yusuke Yoshioka[1],

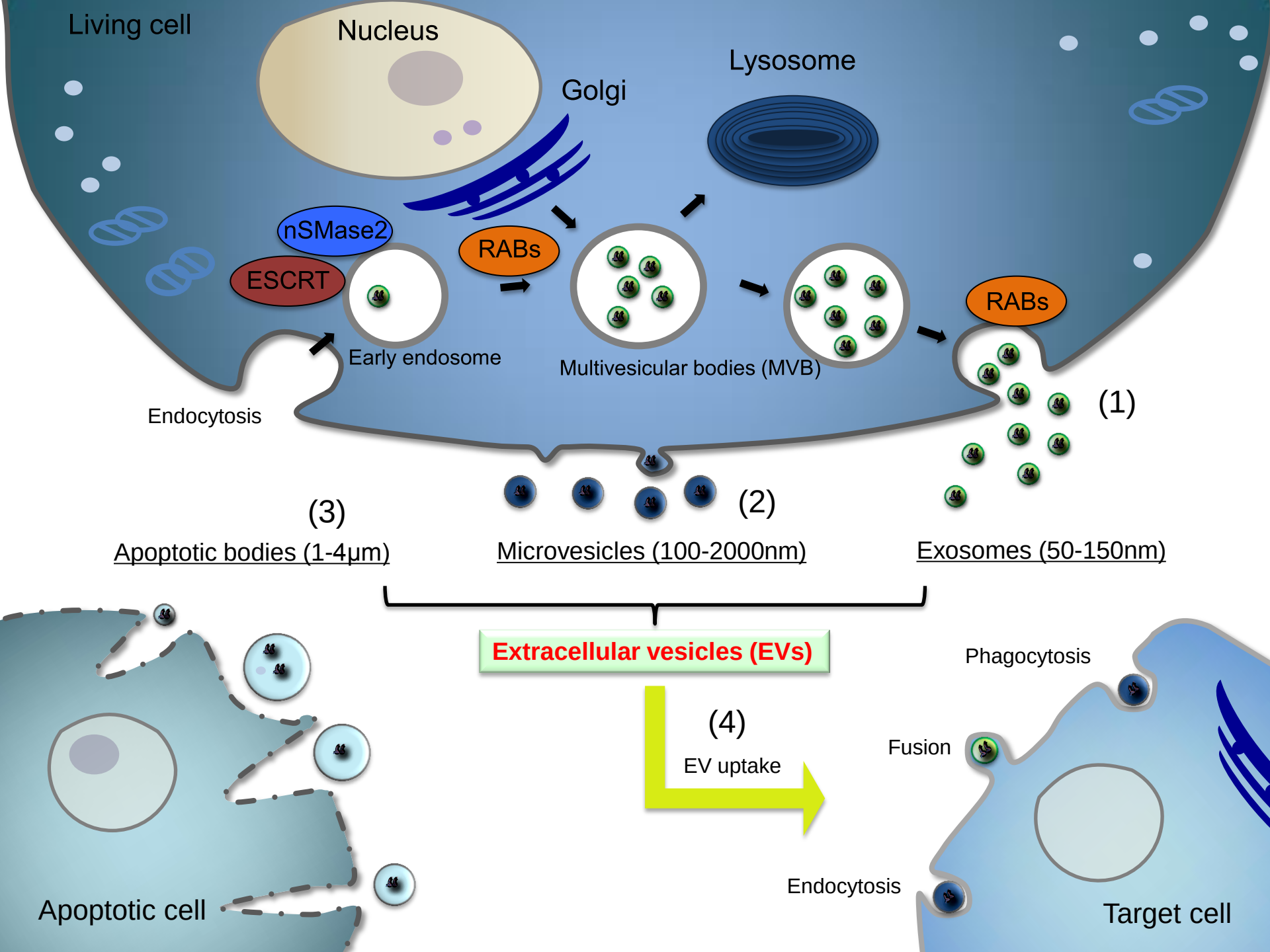
Jun Araya[2], Kazuyoshi Kuwano[2] and Takahiro Ochiya[1]

1) Division of Molecular and Cellular Medicine, National Cancer Center Research Institute

2) Division of Respiratory Disease, Department of Internal Medicine, The Jikei University School of Medicine

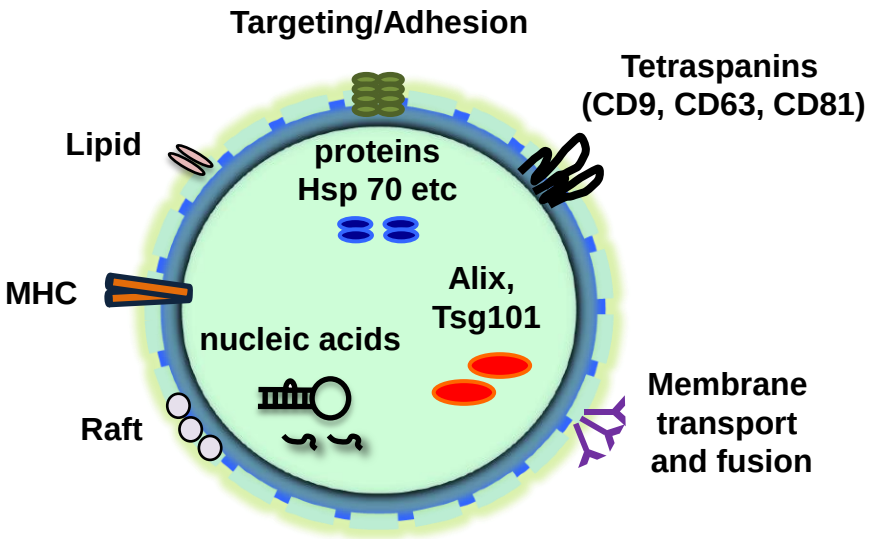
Outline

1. About extracellular vesicles (EVs)
2. Extracellular vesicles in normal airway physiology
3. Extracellular vesicles in COPD pathogenesis
4. Extracellular vesicles in COPD exacerbation
5. Circulating microRNAs and EVs as potential biomarkers for COPD
6. Our work: Suppression of autophagy by extracellular vesicles promotes myofibroblast differentiation in COPD pathogenesis


Living cell
Nucleus
Golgi
Lysosome
nSMase2
ESCRT
RABs
RABs
Early endosome
Multivesicular bodies (MVB)
Endocytosis
(1)
(2)
(3)
Apoptotic bodies (1-4µm)
Microvesicles (100-2000nm)
Exosomes (50-150nm)
Extracellular vesicles (EVs)
(4)
EV uptake
Phagocytosis
Fusion
Endocytosis
Apoptotic cell
Target cell

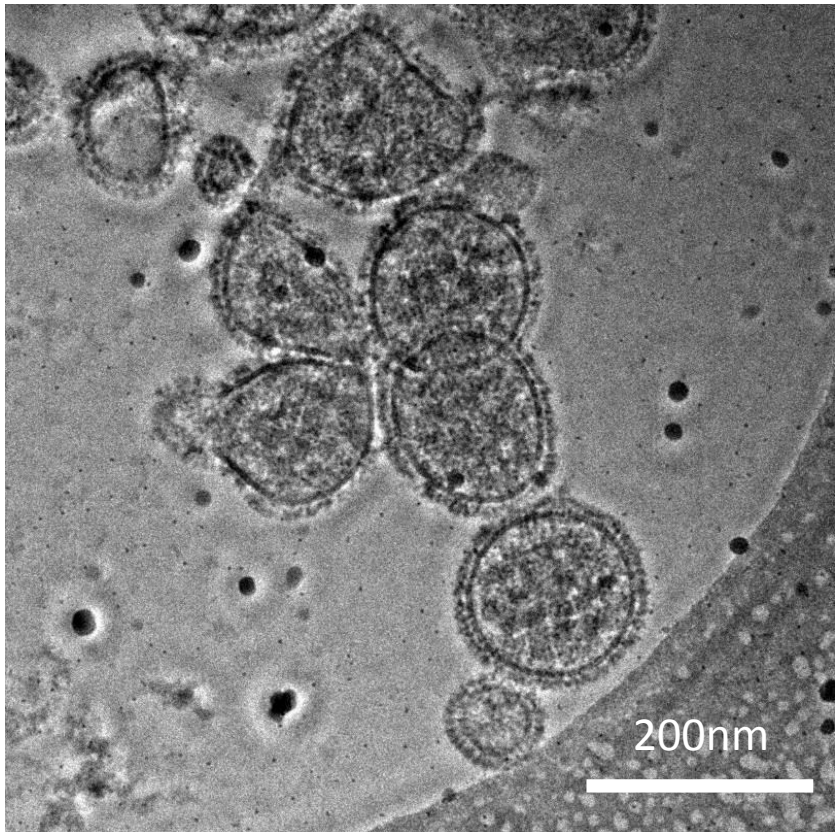
Exosomes

Exosome (40-100 nm)



Phospholipid bilayer-enclosed vesicle

Lung epithelial cell-derived exosomes



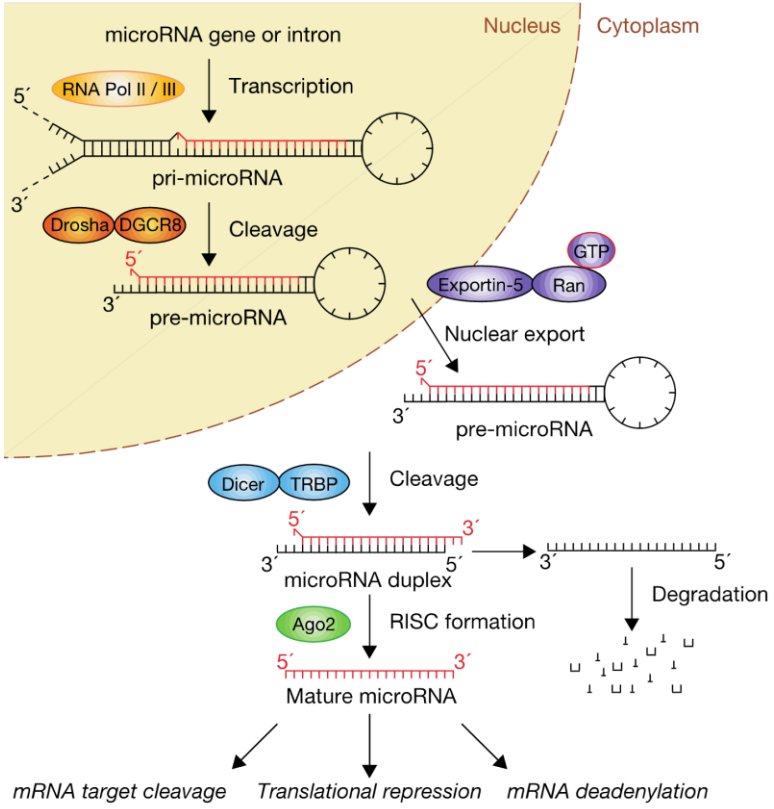
Electron microscopy image

Fujita et al. Trends Mol Med. 2015;21:533.

MicroRNA (miRNA)

MicroRNAs

- are non-coding RNA.
- are small in size with an average length of 22 nucleotides.
- play important roles in regulating the translation and degradation of mRNAs.



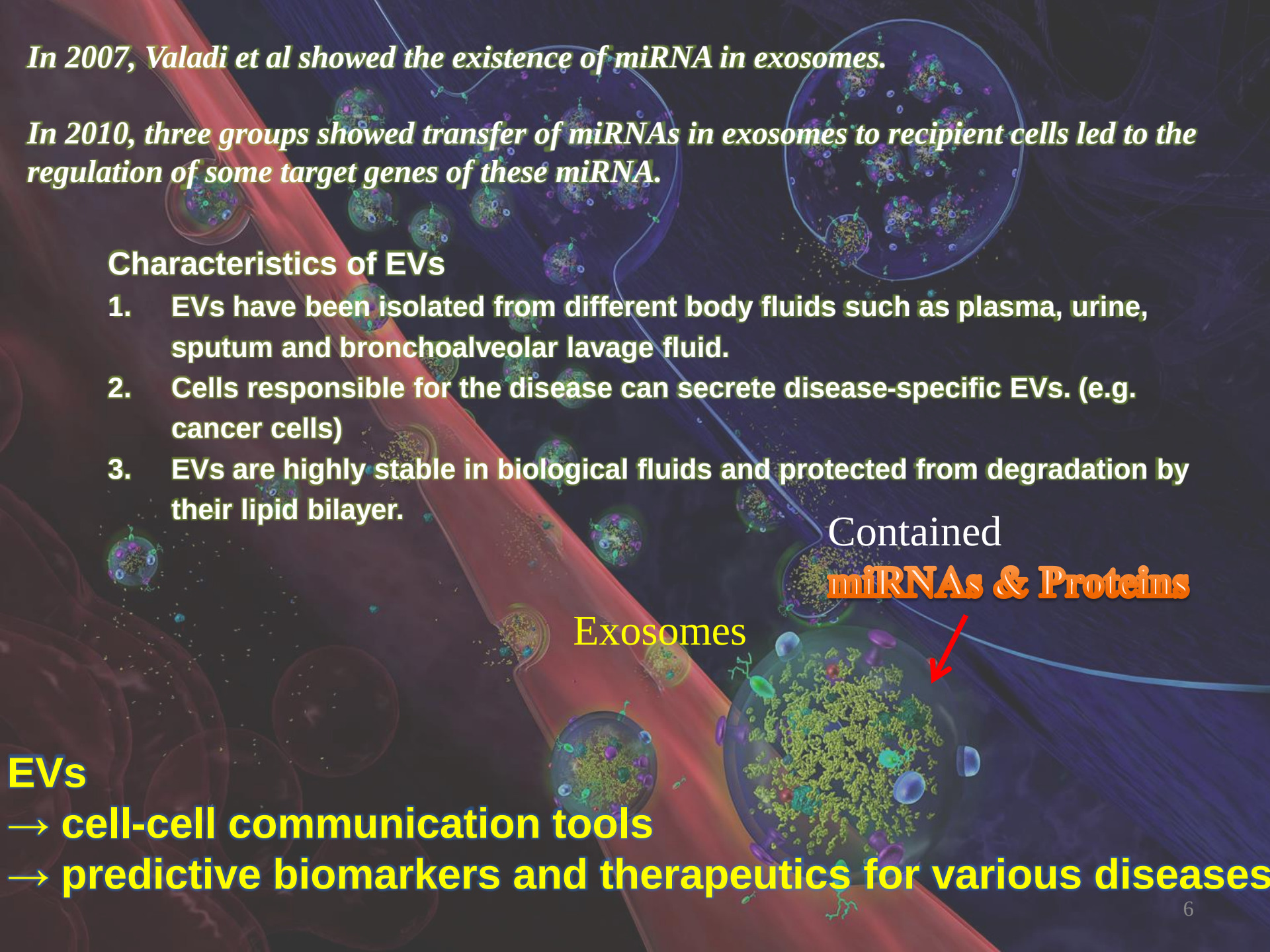
Winter J et al. Nat Cell Biol. 2009;11:228-34.

In 2007, Valadi et al showed the existence of miRNA in exosomes.

In 2010, three groups showed transfer of miRNAs in exosomes to recipient cells led to the regulation of some target genes of these miRNA.

Characteristics of EVs

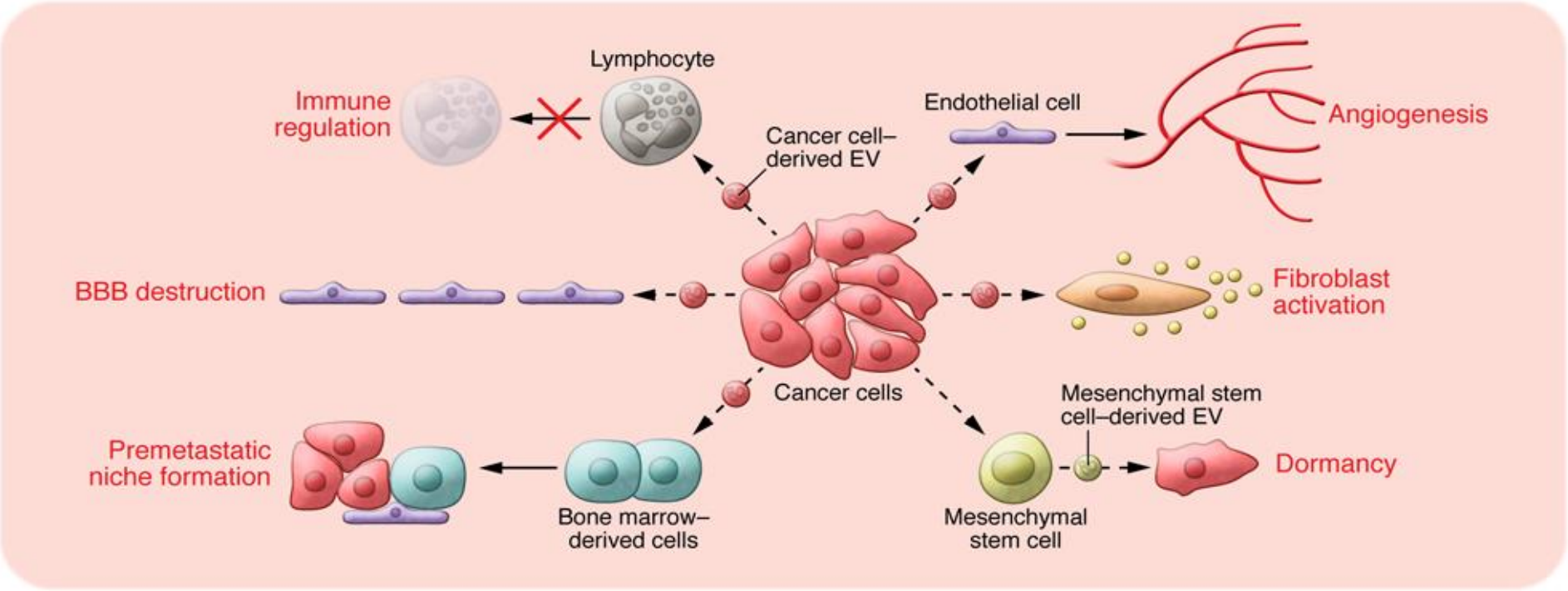
1. EVs have been isolated from different body fluids such as plasma, urine, sputum and bronchoalveolar lavage fluid.
2. Cells responsible for the disease can secrete disease-specific EVs. (e.g. cancer cells)
3. EVs are highly stable in biological fluids and protected from degradation by their lipid bilayer.



EVs
→ cell-cell communication tools
→ predictive biomarkers and therapeutics for various diseases

EVs in Cancers

- There are growing evidences that EVs play a key role in cancer.
- EVs serve as versatile intercellular communication tools.
- Tumor-derived EVs modulate the recipient cell's phenotype such as antigen presentation, apoptosis induction, cellular activation and differentiation.



Kosaka, N, Yoshioka Y, Fujita Y, Ochiya T. J Clin Invest. 2016;126:1-10.

Clinical Applications of EVs

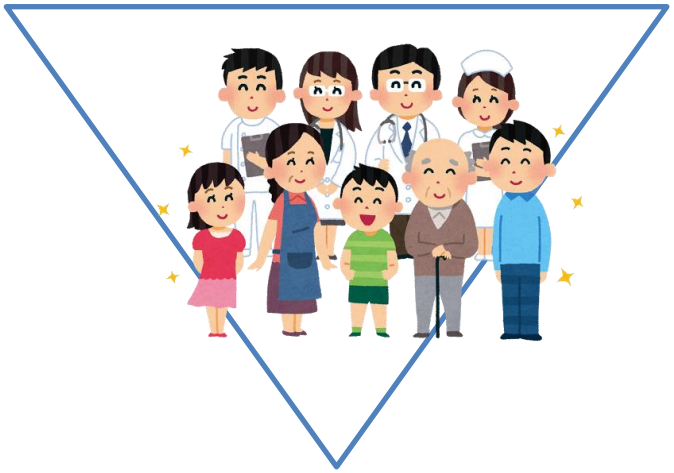
Biomarker

- Companion diagnostics
- Detection of the early stages of diseases (e.g. cancer)

Therapeutics

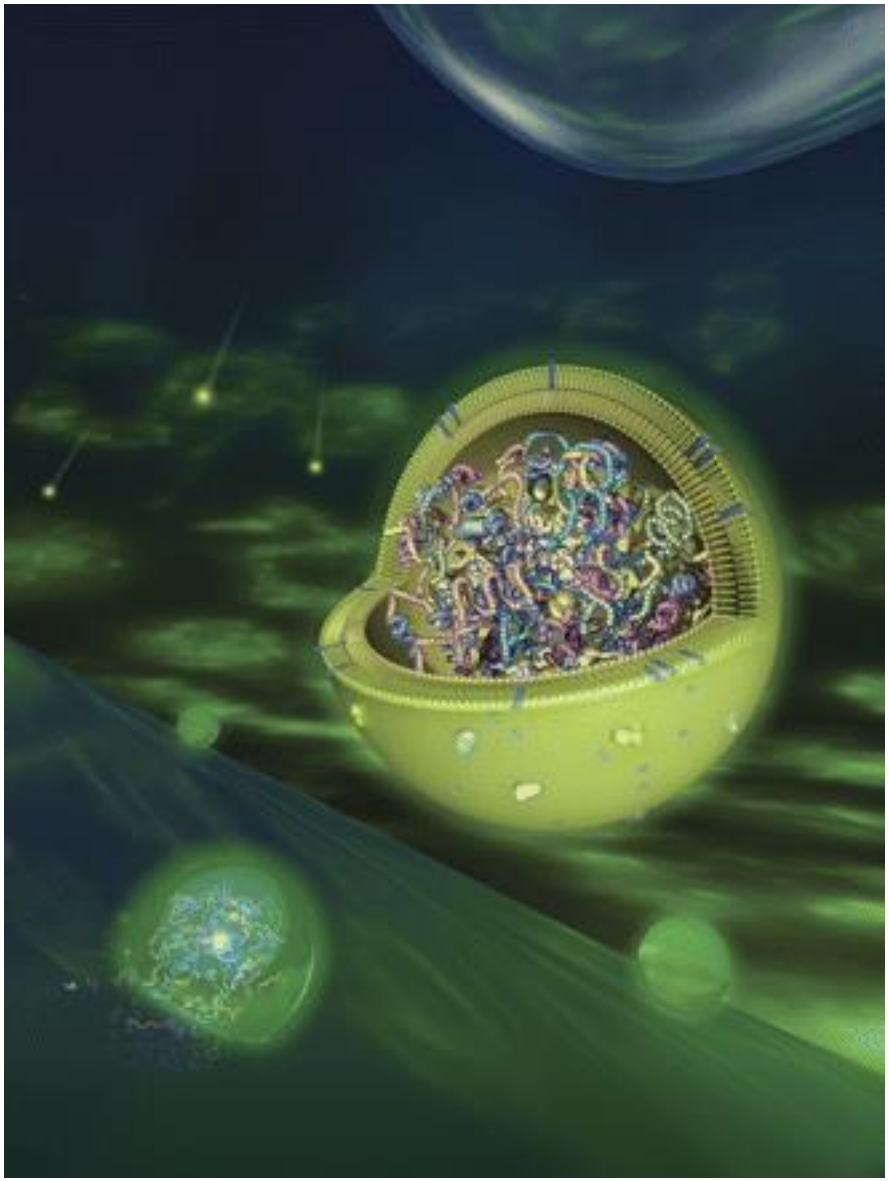
- Vaccine
- Regeneration medicine (applying mesenchymal stem cells)
- Disease specific EV-targeted therapy

etc

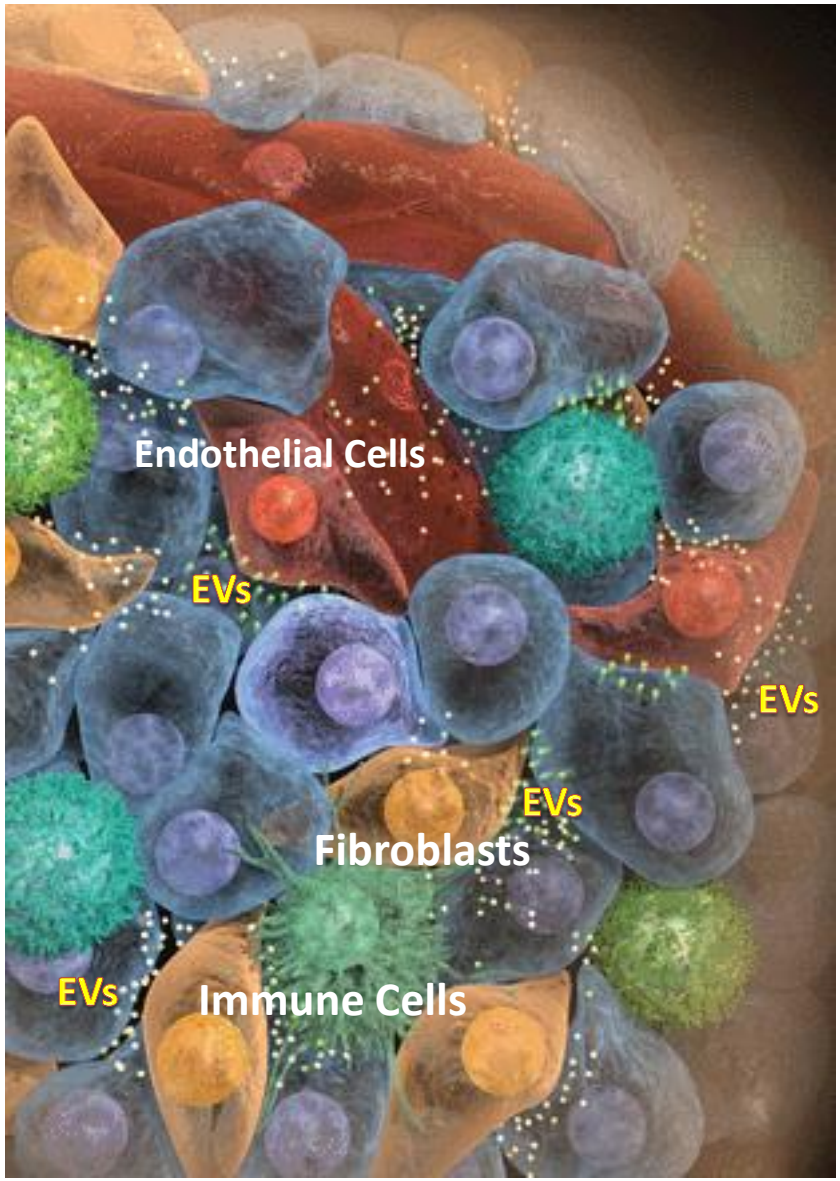


Drug Delivery System

- Loading therapeutically active cargo molecules into EVs
  e.g. Nucleic acid drug



N Kosaka et al. J Biol Chem. 2010;285:17442-52.

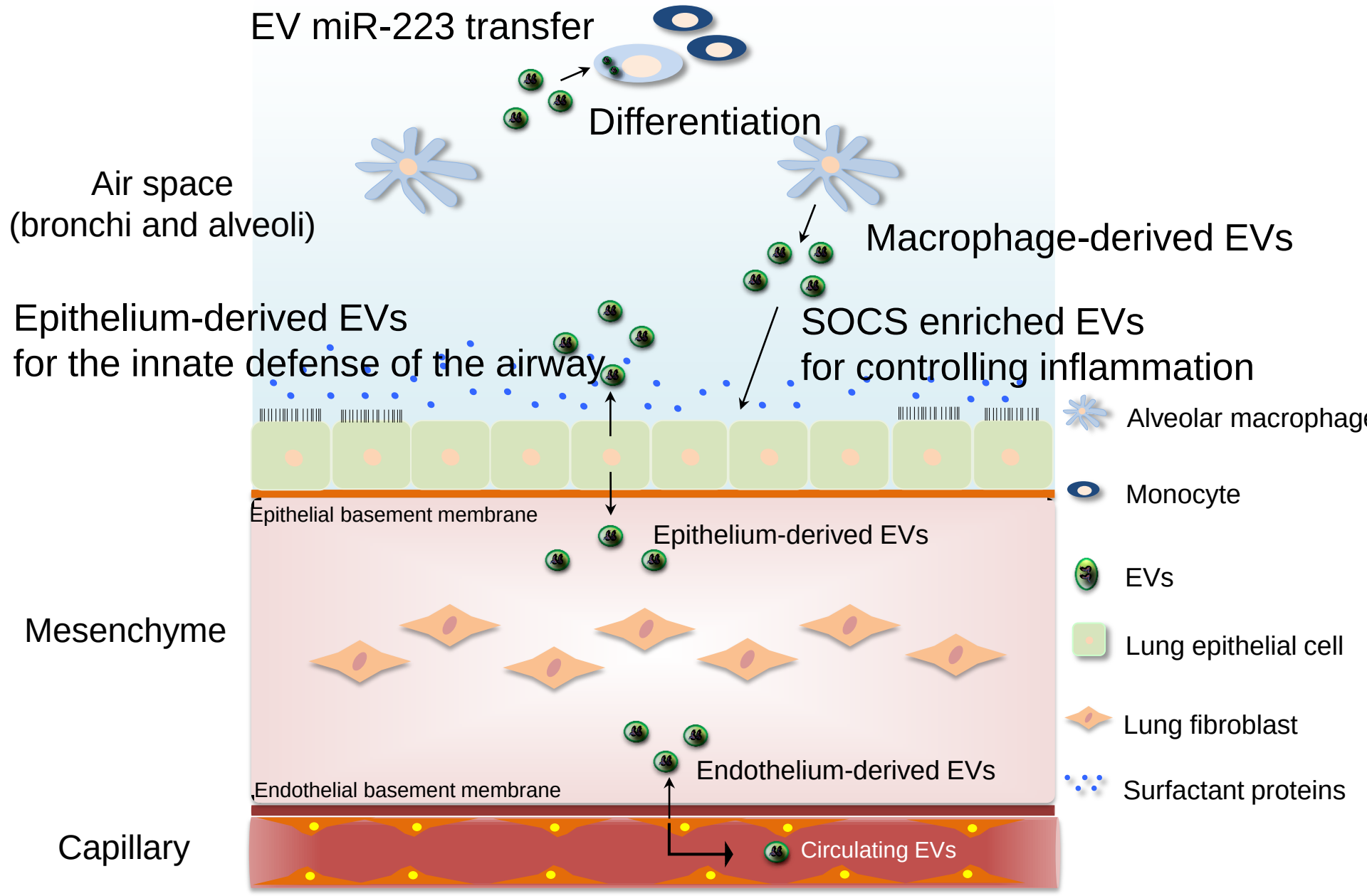


N Kosaka et al. J Biol Chem. 2013;288:10849-59.

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EVs in normal airway physiology



Macrophage-derived EVs

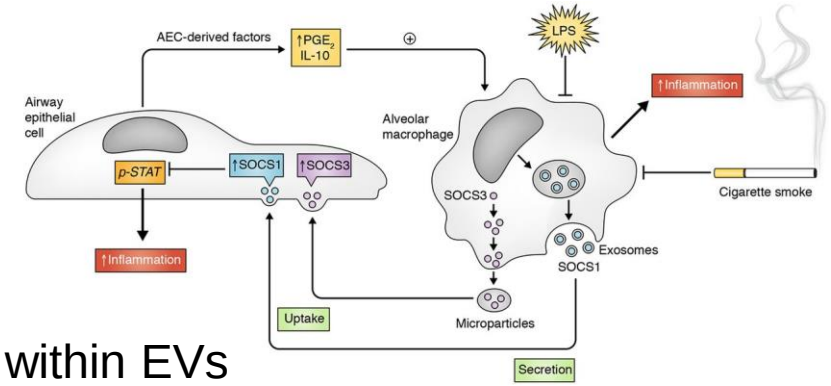
Published April 6, 2015

JEM

Article

Transcellular delivery of vesicular SOCS proteins from macrophages to epithelial cells blunts inflammatory signaling

Emilie Bourdonnay,[1] Zbigniew Zasłona,[1] Loka Raghu Kumar Penke,[1] Jennifer M. Speth,[1] Daniel J. Schneider,[1] Sally Przybranowski,[1] Joel A. Swanson,[2] Peter Mancuso,[3] Christine M. Freeman,[1,4] Jeffrey L. Curtis,[1,5] and Marc Peters-Golden[1]



- Alveolar macrophages can secrete SOCS1,-3 within EVs
- Uptake of these extracellular vesicles by alveolar epithelial cells allowed SOCS1,-3 to suppress STAT signaling following activation by cytokines.
- Exposure to cigarette smoke reduced levels of both SOCS1 and -3.

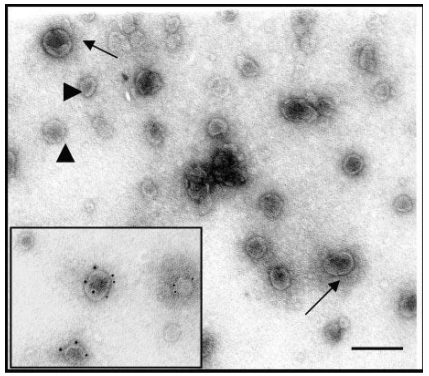
Epithelial cell-derived EVs

The FASEB Journal • Research Communication

Characterization of exosome-like vesicles released from human tracheobronchial ciliated epithelium: a possible role in innate defense

Mehmet Kesimer,* Margaret Scull,† Brian Brighton,‡ Genevieve DeMaria,* Kimberlie Burns,‡ Wanda O'Neal,‡ Raymond J. Pickles,† and John K. Sheehan*,1

*Department of Biochemistry and Biophysics, †Department of Microbiology and Immunology, and ‡Cystic Fibrosis/Pulmonary Research and Treatment Center, University of North Carolina at Chape Hill, Chapel Hill, North Carolina, USA



HTEC derived EVs

Physical characterization and profiling of airway epithelial derived exosomes using light scattering

Mehmet Kesimer *, Richa Gupta

Department of Pathology and Laboratory Medicine, Cystic Fibrosis/Pulmonary Research and Treatment Center, Marsico Lung Institute, University of North Carolina, Chapel Hill, NC 27599-7248, United States

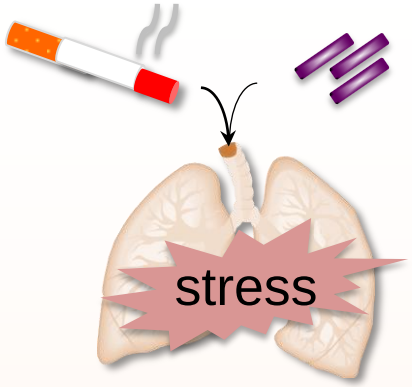
Methods 87 (2015) 59–63

- There are the mucins decoration on the surface of human tracheobronchial epithelial cells (HTEC)–derived EVs.
- The epithelial mucins MUC1, MUC4, and MUC16 contribute to the HTEC-derived EVs structure and these structure have a neutralizing effect on human influenza virus.

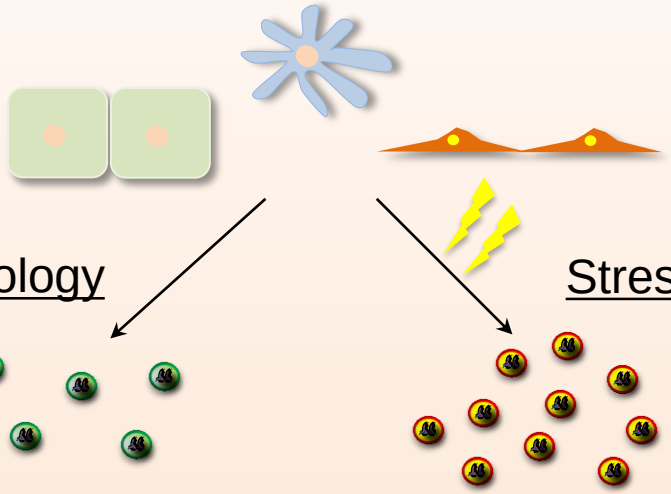
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The Response of EVs in Stress Airway Physiology



Infection, cigarette smoke, DNA damage, oxidative stress, etc



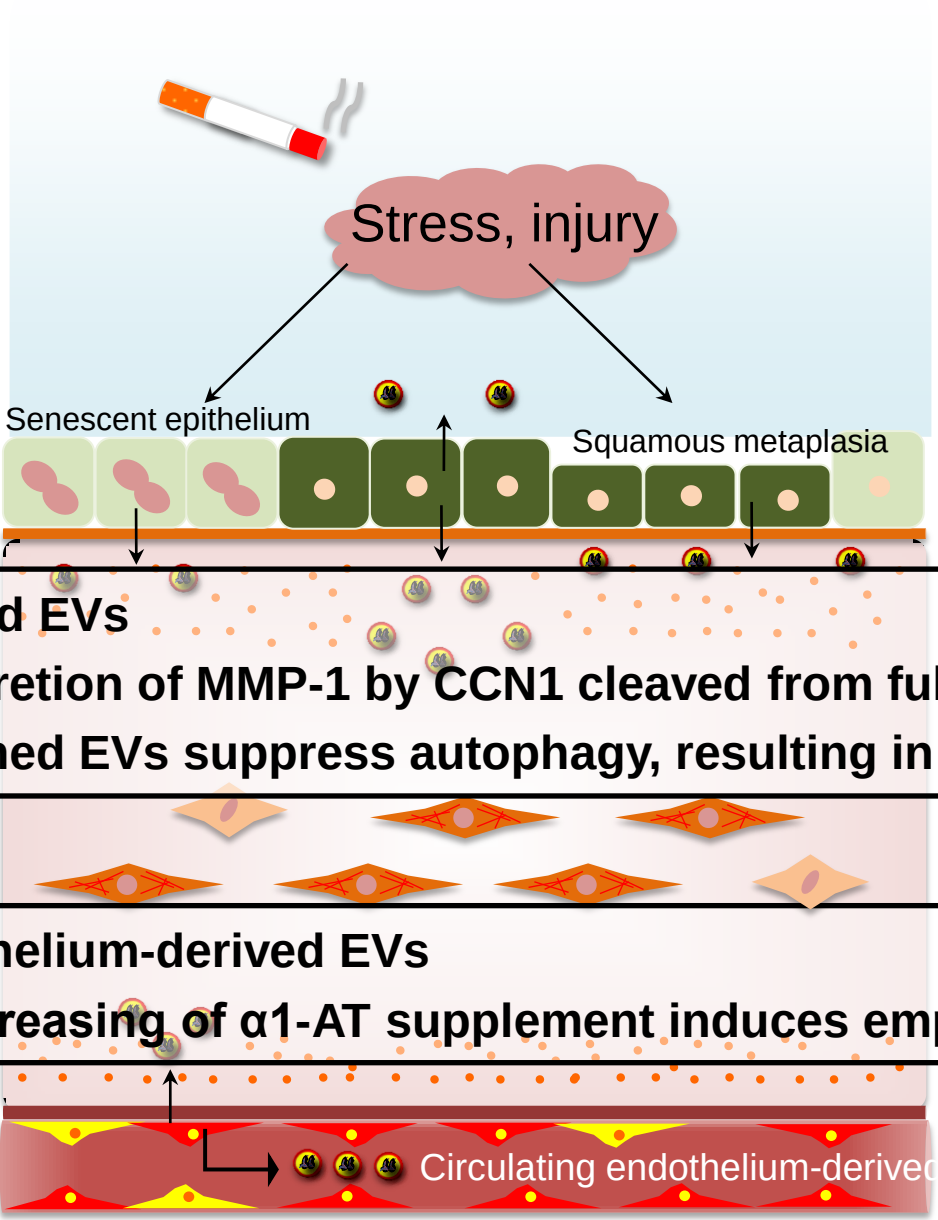
Normal physiology

To maintain homeostasis
through the EV cargo

Stress physiology

1) modified EV compositions
(proinflammatory functions)
2) EV secretion enhanced
(by various secretion mechanisms)

The Roles of EVs in Cigarette Smoke Induced COPD



Epithelium-derived EVs

1) **Activating secretion of MMP-1 by CCN1 cleaved from full length CCN1 in EVs**
2) **miR-210 enriched EVs suppress autophagy, resulting in airway remodeling**

Endothelium-derived EVs

- **Decreasing of α1-AT supplement induces emphysema**

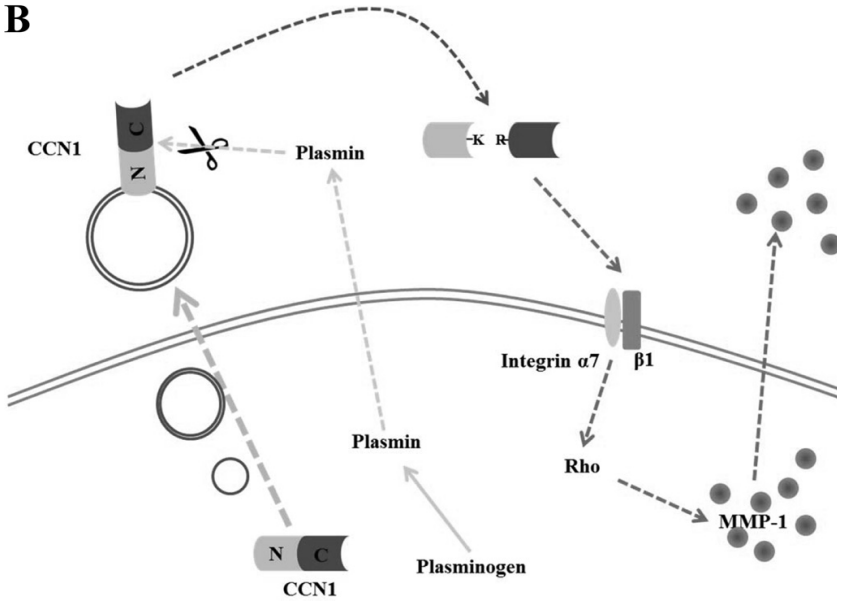
First published June 27, 2014; doi:10.1152/ajplung.00102.2014.

CCN1 secretion and cleavage regulate the lung epithelial cell functions after cigarette smoke

Am J Physiol Lung Cell Mol Physiol 307: L326–L337, 2014.

Hyung-Geun Moon,[1] Sang-Heon Kim,[1,2] Jinming Gao,[3] Taihao Quan,[4] Zhaoping Qin,[4] Juan C. Osorio,[1] Ivan O. Rosas,[1,6] Min Wu,[5] Yohannes Tesfaigzi,[6] and Yang Jin[1]

- Cigarette smoke extract induced CCN1-enriched EVs from epithelial cells.
- The EVs-mediated secretion of full-length CCN1(flCCN1) potentially allows inflammatory signals to be transmitted to distant portions of the lung.
- Prolonged Cigarette smoke exposure cleaved the flCCN1 in EVs into truncated form (cCCN) by CS-upregulated plasmin.
- cCCN interacts with integrin-α7 and activates the secretion of MMP1 in lung epithelial cells via the Rho pathway.



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PLOS ONE

Active Trafficking of Alpha 1 Antitrypsin across the Lung Endothelium

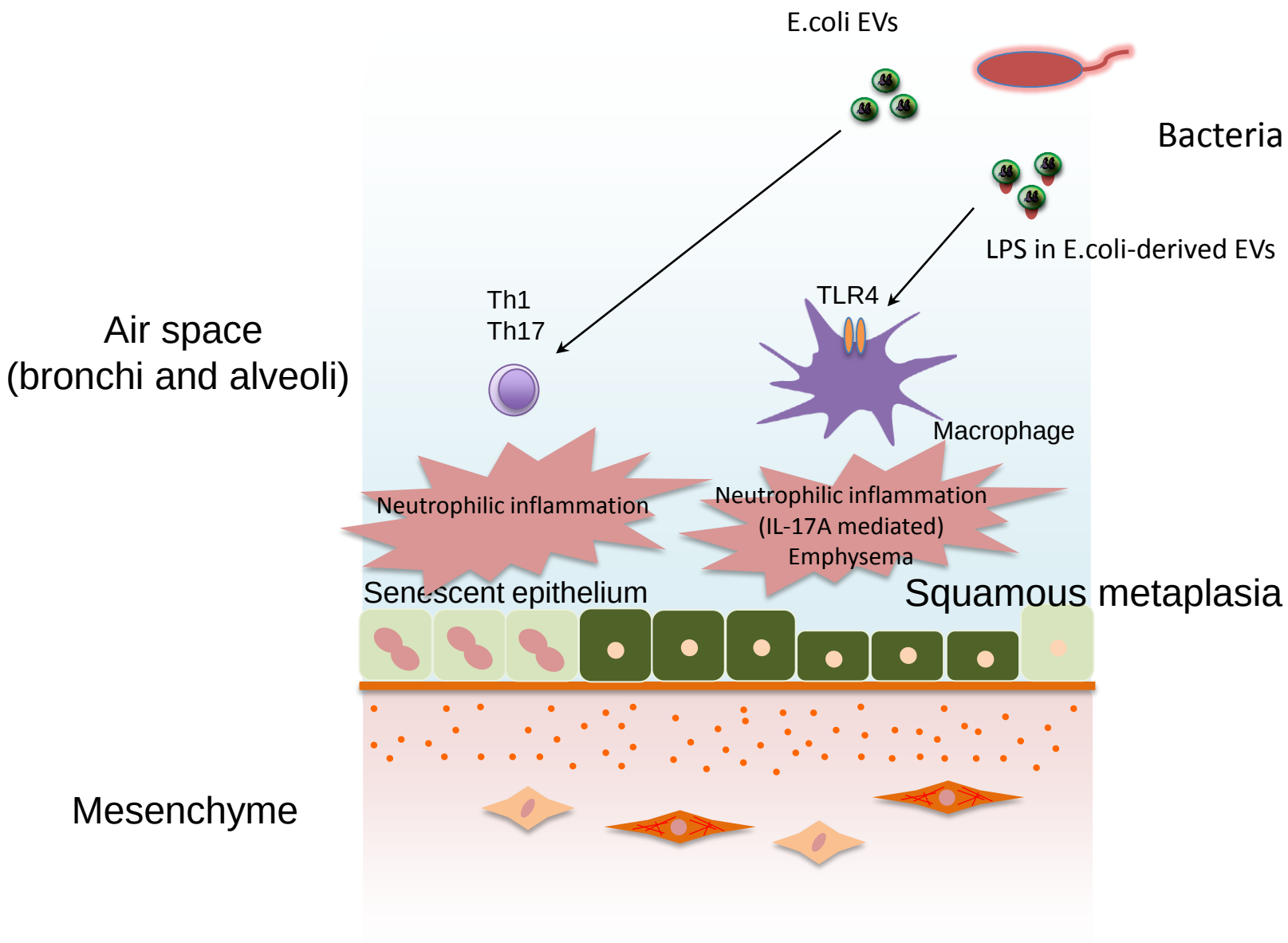
Angelia D. Lockett[1]*, Mary Beth Brown[2], Nieves Santos-Falcon[4], Natalia I. Rush[1], Houssam Oueini[1], Amber J. Oberle[1], Esther Bolanis[1], Miryam A. Fragoso[4], Daniela N. Petrusca[1], Karina A. Serban[1], Kelly S. Schweitzer[1], Robert G. Presson Jr.[3], Michael Campos[4☯], Irina Petrache[1,5☯]

April 2014 | Volume 9 | Issue 4 | e93979

- AAT internalized by lung epithelial cells and protect lung from elastase, inflammation, and endothelial cell apoptosis.
- Lung endothelial cells assist not only in AAT transcytosis but also in its release into the alveolar epithelial cells via EVs.
- Cigarette smoke exposure inhibits AAT transport into epithelial cells.

AAT: Alpha-1 antitrypsin

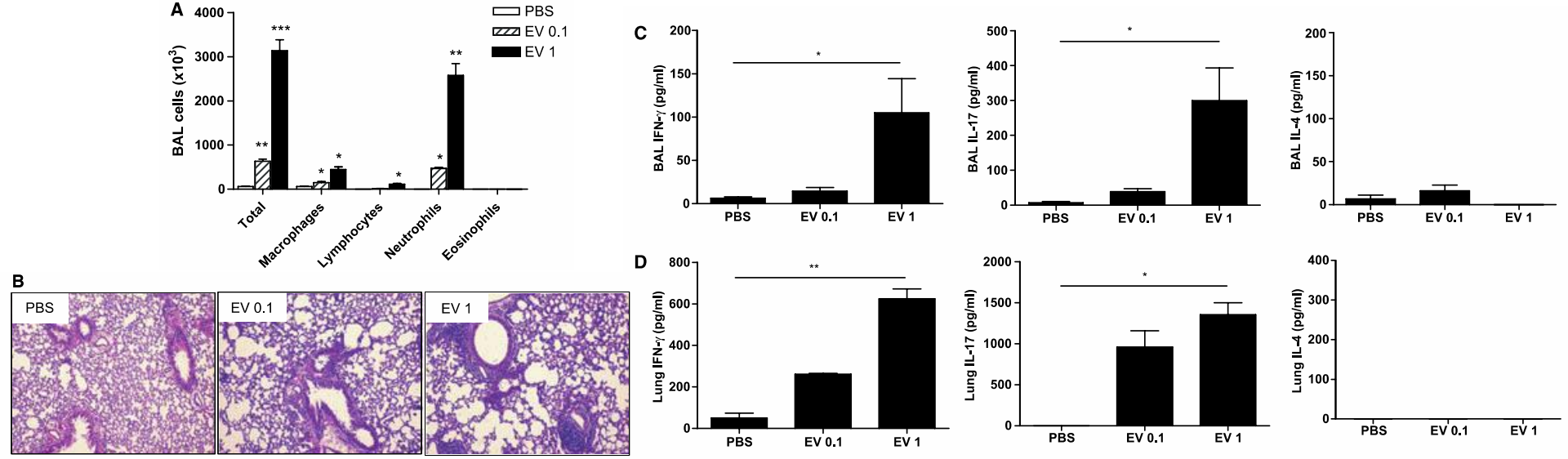
Bacteria-derived EVs in COPD pathogenesis



Staphylococcus aureus-derived extracellular vesicles induce neutrophilic pulmonary inflammation via both Th1 and Th17 cell responses

M.-R. Kim[1,*], S.-W. Hong[1,*], E.-B. Choi[1], W.-H. Lee[1], Y.-S. Kim[1], S. G. Jeon[1], M. H. Jang[2], Y. S. Gho[1] & Y.-K. Kim[1]

Allergy. 2012;67:1271-81.



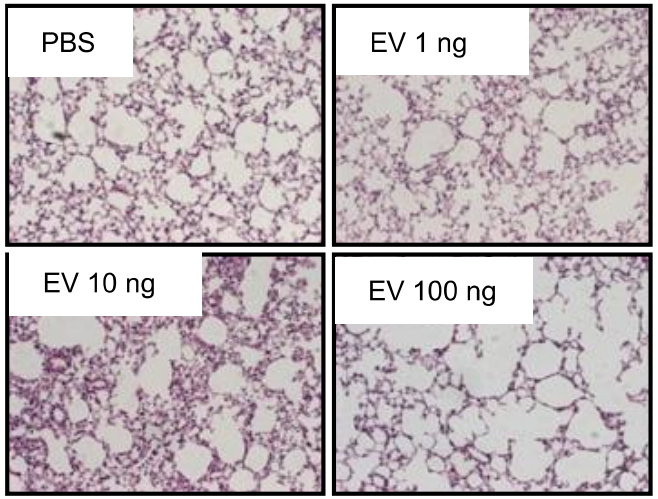
- Repeated inhalation of Staphylococcus aureus-derived EVs induced pulmonary inflammation cells, especially neutrophil.
- Repeated inhalation of the EVs induced the both Th1 (IFN-γ) and Th17(IL-17) cytokines.
- Immune responses induces by the EVs are dependent on TLR2 signaling.

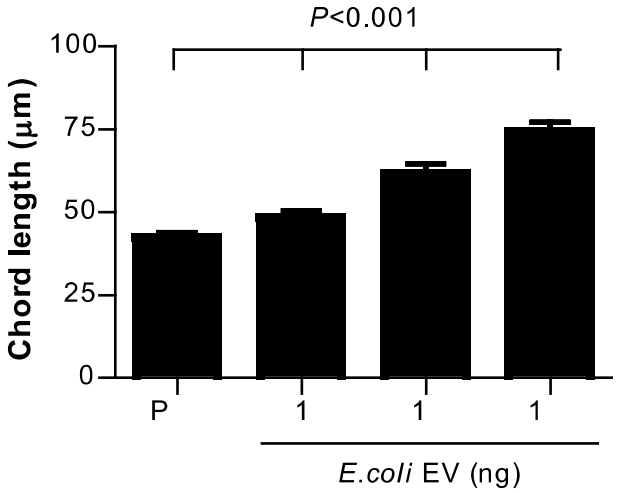
Journal of Immunology, 2015, 194: 3361–3368.

Extracellular Vesicles Derived from Gram-Negative Bacteria, such as *Escherichia coli*, Induce Emphysema Mainly via IL-17A–Mediated Neutrophilic Inflammation

You-Sun Kim,*,†,1 Won-Hee Lee,‡,1 Eun-Jeong Choi,‡,1 Jun-Pyo Choi,§,1 Young Joo Heo,* Yong Song Gho,‡ Young-Koo Jee,¶ Yeon-Mok Oh,*,† and Yoon-Keun Kim§

- Airway exposure to E.coli derived EVs, one of the Gram-negative bacteria, can induce neutorophilic inflammation and emphysema mainly in an IL-17a-dependent manner.
- E.coli-derived EVs uptake by inflammatory cells such as macrophages is dependent on both LPS and TLR4 signaling.





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ORIGINAL ARTICLE

Increased circulating endothelial microparticles in COPD patients: a potential biomarker for COPD exacerbation susceptibility

Toru Takahashi,[1,2] Seiichi Kobayashi,[3] Naoya Fujino,[1] Takaya Suzuki,[4] Chiharu Ota,[1] Mei He,[1] Mitsuhiro Yamada,[5] Satoshi Suzuki,[6] Masaru Yanai,[3] Shin Kurosawa,[2] Mutsuo Yamaya,[1] Hiroshi Kubo[1]

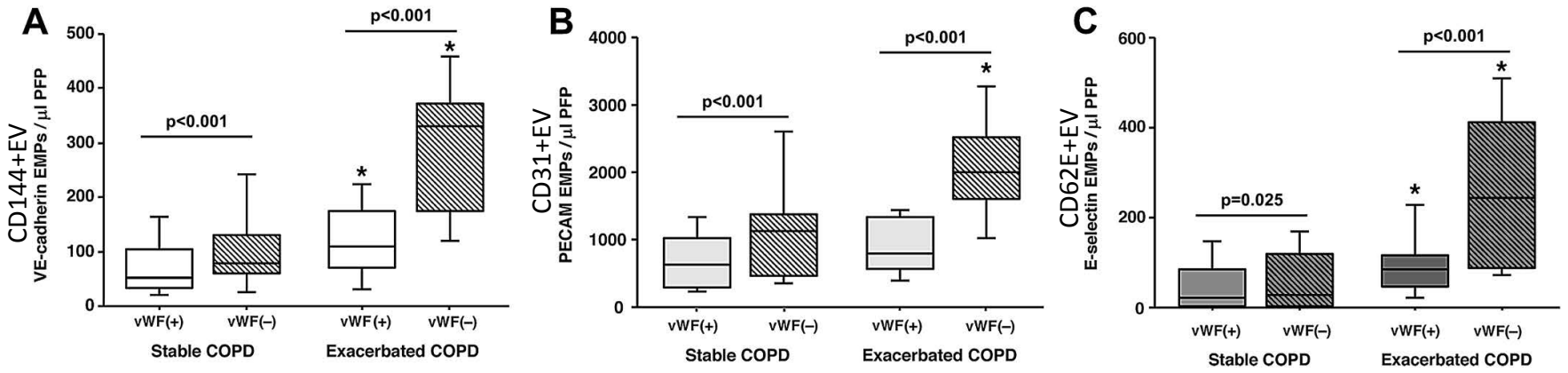


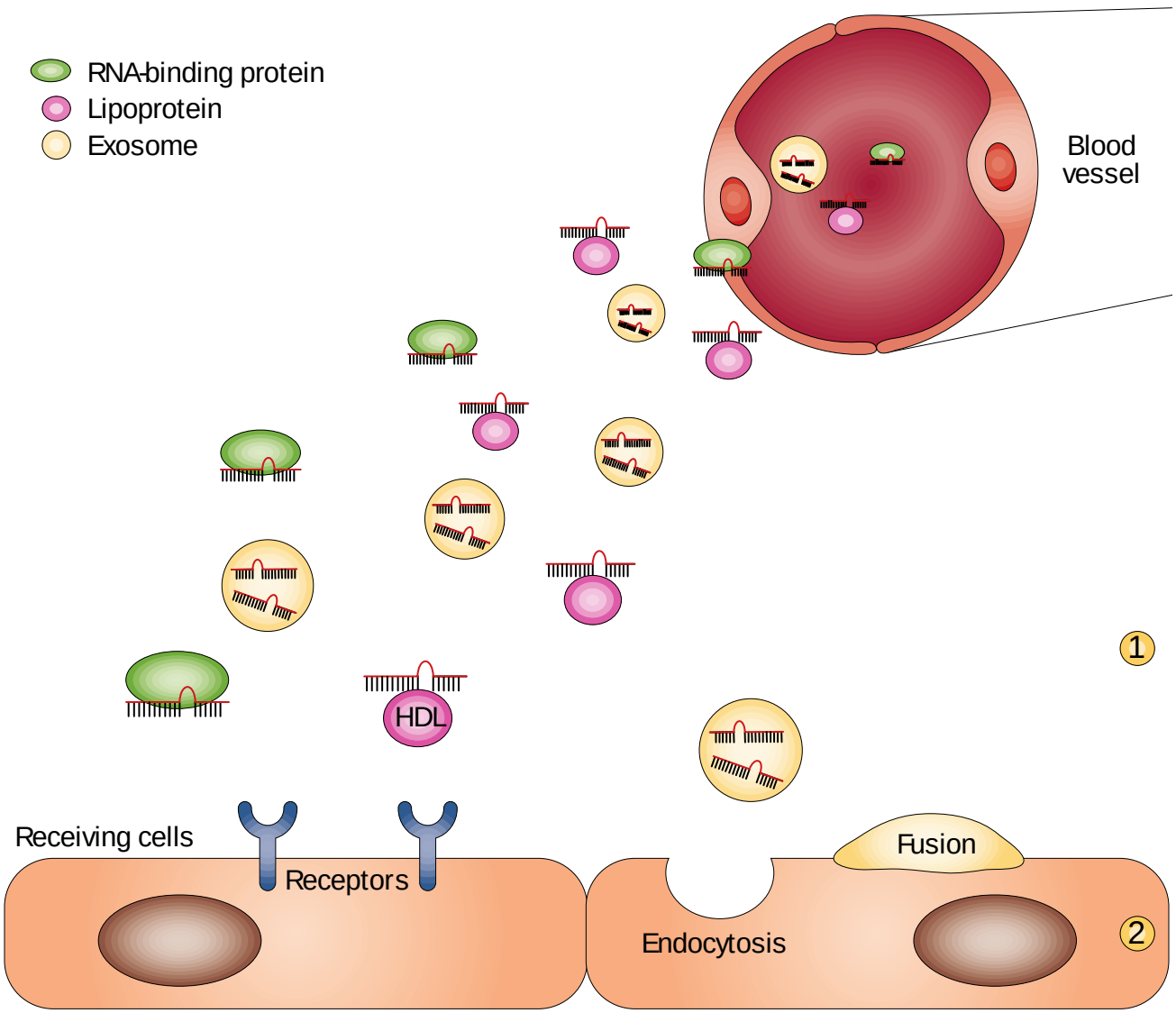
Figure 3 Comparison of the EMP numbers in stable GOLD stage II patients and those with exacerbation. (A) VE-cadherin EMPs, (B) PECAM EMPs, (C) E-selectin EMPs. *, $p<0.05$ vs. stable COPD.

CD144+EV, 31+EV, 62E+EVs were significantly higher in patients during COPD exacerbation than in stable patients.

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Circulating microRNA



Guay C et al.Nat Rev Endocrinol. 2013;9:513.

Potential Biomarkers for COPD

Body fluids	Potential biomarkers	Detection methods	References
microRNAs			
Serum	miR-21 / miR-181a ratio	Realtime PCR	Mol Biosyst 2014
Serum	Upregulated: miR-7 Downregulated: miR-20a, -28-3p, -34c-5p, -100	Realtime PCR	Exp Lung Res. 2012
Sputum	Downregulated: let-7c, miR-125b , -150, -146a, -449, -203, -222, -340	Realtime PCR	Am J Respir Crit Care Med 2011
Exhaled breath condensates	Downregulated: let-7a, miR-328, miR-21	Realtime PCR	J Allergy Clin Immunol 2013
EVs			
Plasma	CD31+EMPs, CD31+ / CD62+ EMPs ratio,	Flow cytometry	Am J Respir Crit Care Med 2011
Plasma	CD31+EMPs, CD62E+EMPs	Flow cytometry	Am J Respir Crit Care Med. 2011
Plasma	CD144+EMPs, CD31+EMPs, CD62E+EMPs	Flow cytometry	Thorax. 2012
Sputum	CD31+EMPs, CD66+EMPs, CD235ab+EMPs	Flow cytometry	Int J Chron Obstruct Pulmon Dis. 2016

MicroRNA Expression in Induced Sputum of Smokers and Patients with Chronic Obstructive Pulmonary Disease

Geert R. Van Pottelberge[1]*, Pieter Mestdagh[2]*, Ken R. Bracke[1], Olivier Thas[3], Yannick M. T. A. van Durme[1], Guy F. Joos[1], Jo Vandesompele[2], and Guy G. Brusselle[1]

TABLE 5. DIFFERENTIAL miRNA EXPRESSION IN VALIDATION COHORT

	A. Current Smokers without COPD vs. Never-Smokers		B. Current Smokers with COPD vs. Never-Smokers		C. Current Smokers with COPD vs. Current Smokers without COPD		D. Current Smokers with COPD vs. Ex-Smokers with COPD	
MicroRNA ID	Fold Change	P Value	Fold Change	P Value	Fold Change	P Value	Fold Change	P Value
let-7c	1.13	0.450	2 2.94	0.007	2 3.24	0.004	2 3.25	0.009
miR-125b	1.26	0.112	2 2.93	0.041	2 3.63	0.019	2 3.13	0.057
miR-150	1.49	0.151	2 4.99	0.023	2 7.36	0.003	2 7.14	0.017
miR-146a	2 1.07	0.597	2 8.33	0.008	2 7.69	0.007	2 7.15	0.011
miR-449	2 1.07	0.650	2 1.75	0.364	2 1.62	0.326	2 3.57	0.035
miR-203	2 1.66	0.496	2 8.62	0.001	2 6.06	0.003	2 16.0	0.001
miR-340	2 1.40	0.041	2 1.08	0.705	2 1.29	0.174	1.15	0.360
miR-222	2 1.75	1.00	2 1.23	0.705	1.41	0.940	2 3.48	0.003

- miRNAs can be measured in induced sputum supernatant.
- Cigarette smoking has a significant influence on miRNA expression.
- Several miRNAs are associated with the severity of airway obstruction in COPD, independent of smoking.

Endothelial Microparticles in Mild Chronic Obstructive Pulmonary Disease and Emphysema

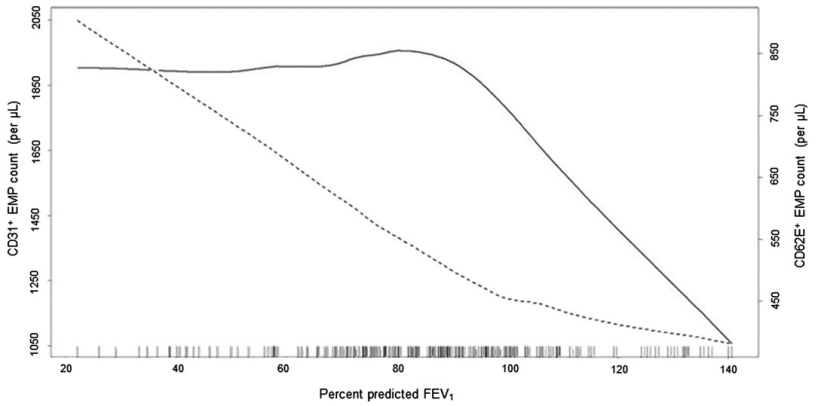
The Multi-Ethnic Study of Atherosclerosis Chronic Obstructive Pulmonary Disease Study

Michael A. Thomashow[1]*, Daichi Shimbo[1]*, Megha A. Parikh[1], Eric A. Hoffman[2], Jens Vogel-Claussen[3,4], Katja Hueper[3,4], Jessie Fu[1], Chia-Ying Liu[3], David A. Bluemke[3,5], Corey E. Ventetuolo[6], Margaret F. Doyle[7], and R. Graham Barr[1,8]

Am J Respir Crit Care Med. 2013;188:60-8.

TABLE 2. ENDOTHELIAL MICROPARTICLE COUNTS BY COPD SEVERITY

	Control Subjects ($n = 76$)	Mild ($n = 39$)	Moderate ($n = 45$)	Severe ($n = 19$)	*P* Value for Linear Trend Across COPD Severity
$CD31^+$ endothelial microparticles per microliter, log-transformed					
Mean (SD)	7.11 (0.58)	7.12 (0.49)	7.26 (0.71)	7.52 (0.51)	0.01
Predicted mean, model 1*	7.10	7.30	7.27	7.49†	0.02
Predicted mean, model 2‡	7.10	7.32†	7.30	7.51†	0.01
Predicted mean, model 3§	7.07	7.31†	7.27	7.40†	0.03
$CD51^+$ endothelial microparticles per microliter, log-transformed					
Mean (SD)	6.80 (0.79)	6.91 (0.68)	6.94 (0.78)	7.17 (0.83)	0.07
Predicted mean, model 1	6.80	7.06	6.89	7.00	0.43
Predicted mean, model 2	6.80	7.08	6.94	7.02	0.80
Predicted mean, model 3	6.71	7.12†	6.85	6.83	0.47
$CD62E^+$ endothelial microparticles per microliter, log-transformed					
Mean (SD)	5.98 (0.62)	6.09 (0.68)	6.02 (0.71)	6.35 (0.69†)	0.047
Predicted mean, model 1	5.98	6.15	6.11	6.53†	0.05
Predicted mean, model 2	5.98	6.16	6.12	6.54†	0.05
Predicted mean, model 3	5.98	6.22	6.11	6.51†	0.03

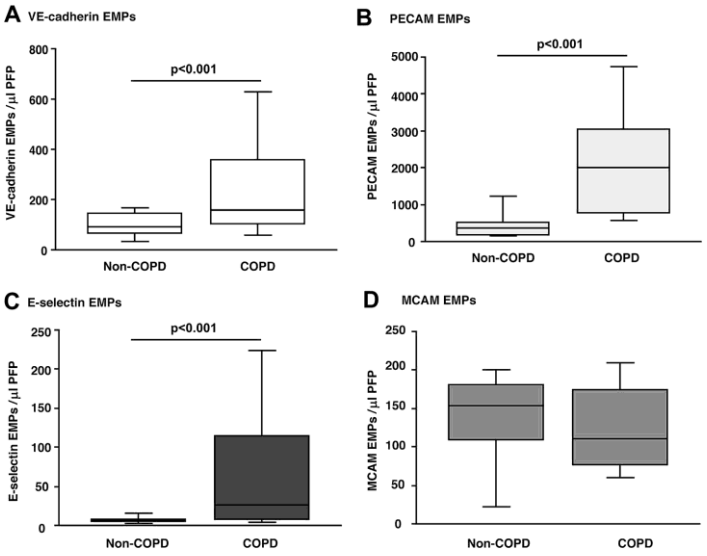


- Endothelial cell-derived EVs in plasma were analyzed.
- CD31+EVs, suggestive of endothelial cell apoptosis, were elevated in mild COPD and emphysema.
- CD62E+EVs indicative of endothelial activation were elevated in severe COPD.

ORIGINAL ARTICLE

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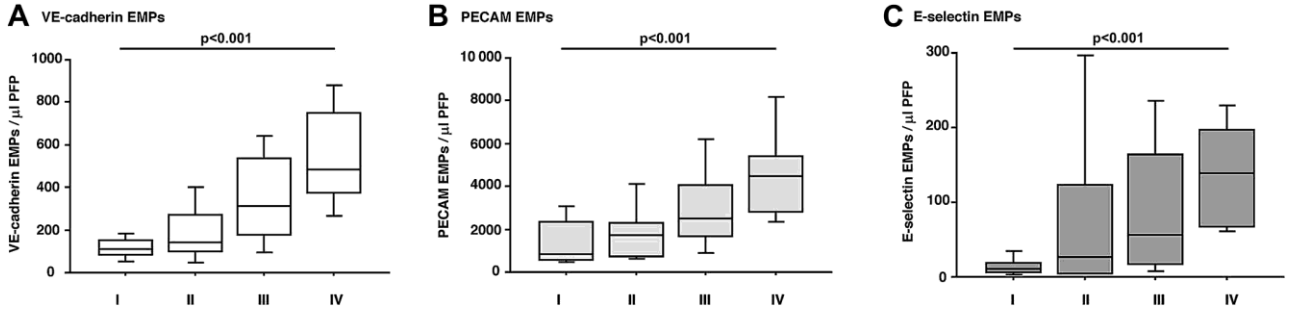


Figure 2 Comparison of the EMP numbers among GOLD stages. (A) VE-cadherin EMPs, (B) PECAM EMPs, (C) E-selectin EMPs.

- Endothelial cell-derived EVs in plasma were analyzed.
- The numbers of CD144+EVs, CD31+EVs, CD62E+EVs were significantly higher in the stable COPD patients than in the non-COPD volunteers.

Outline

1. About extracellular vesicles (EVs)
2. Extracellular vesicles in normal airway physiology
3. Extracellular vesicles in COPD pathogenesis
4. Extracellular vesicles in COPD exacerbation
5. Circulating miRNAs and EVs as potential biomarkers for COPD
6. Our work: Suppression of autophagy by extracellular vesicles promotes myofibroblast differentiation in COPD pathogenesis

Mechanisms Underlying Airflow Limitation in COPD

Small Airways Disease

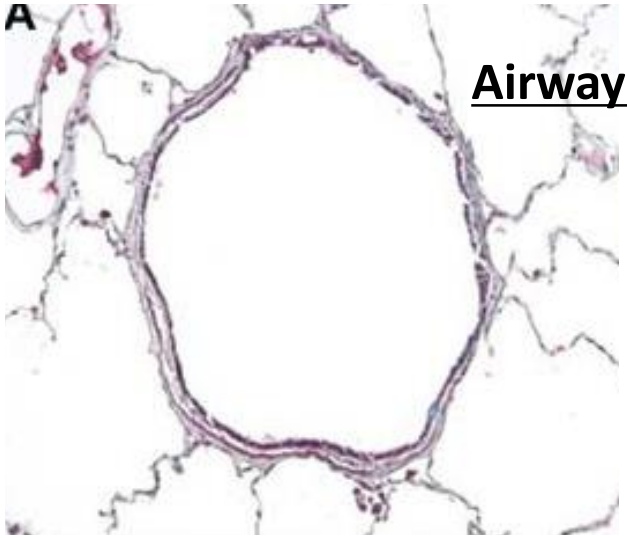
- Airway inflammation
- Airway fibrosis, luminal plugs
- Increased airway resistance

Parenchymal Destruction

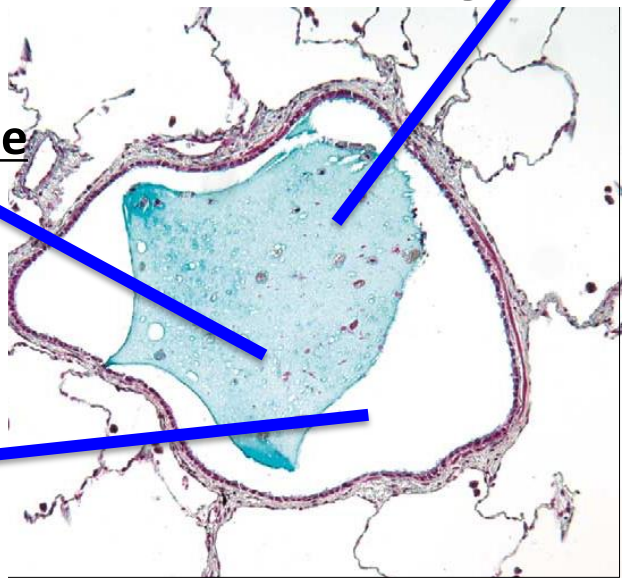
- Loss of alveolar attachments
- Decrease of elastic recoil

AIRFLOW LIMITATION

normal lung



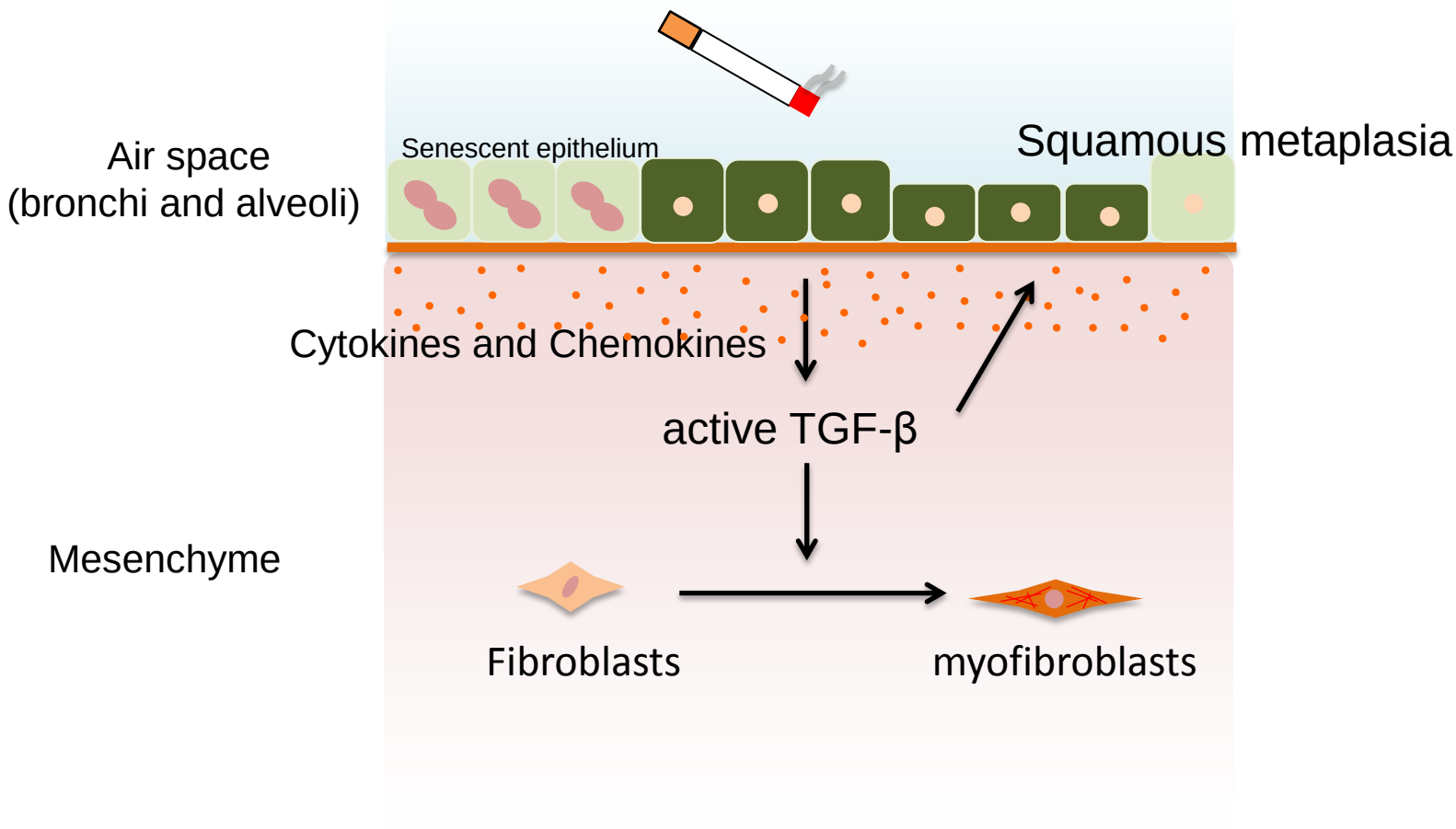
COPD lung



James C Hogg. Lancet 2004; 364: 709–21

Small Airway Remodeling

The interaction between bronchial epithelial cell and fibroblast



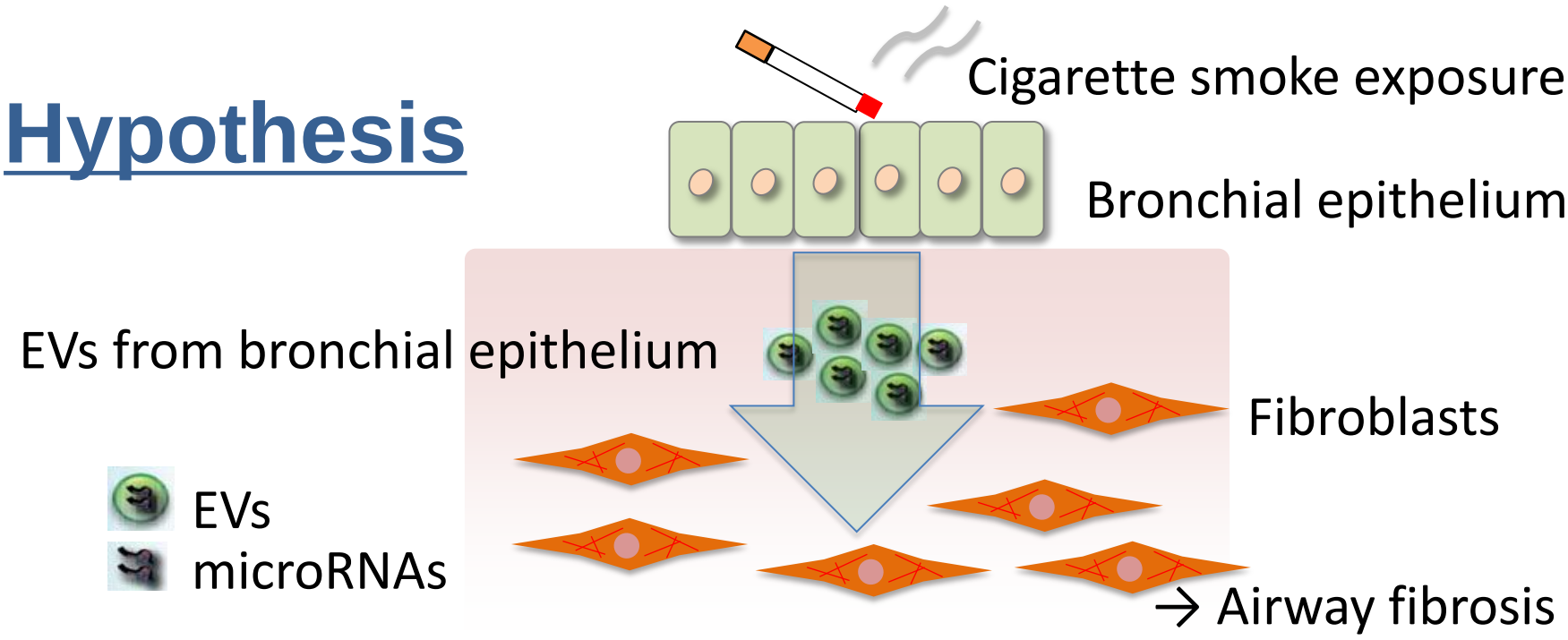


Do smoking-trigged bronchial epithelial cell-derived EV and EV miRNAs influence lung fibroblasts (airway remodeling)??

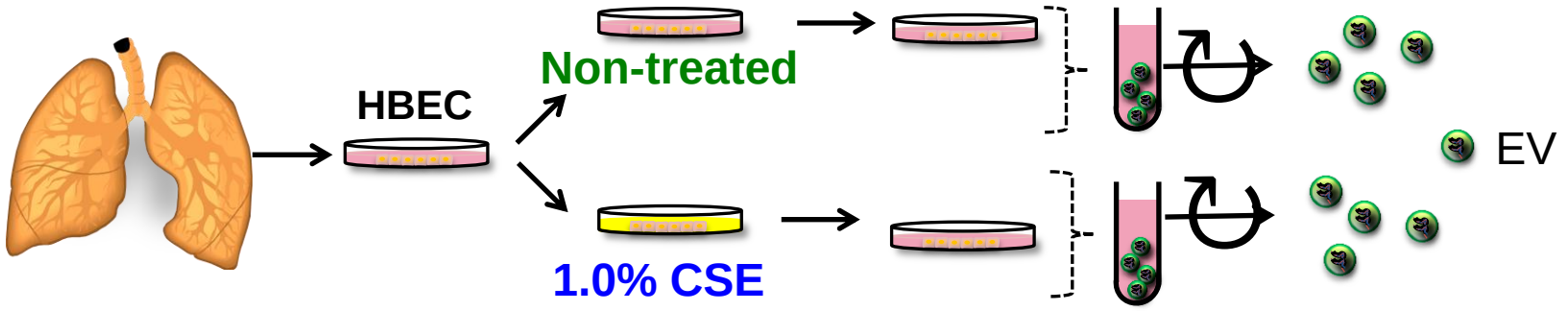
Objective

- To reveal the involvement of extracellular vesicles (EVs)-mediated intercellular communication between bronchial epithelial cells and lung fibroblasts in the mechanisms for airway fibrotic remodeling during COPD pathogenesis

Hypothesis



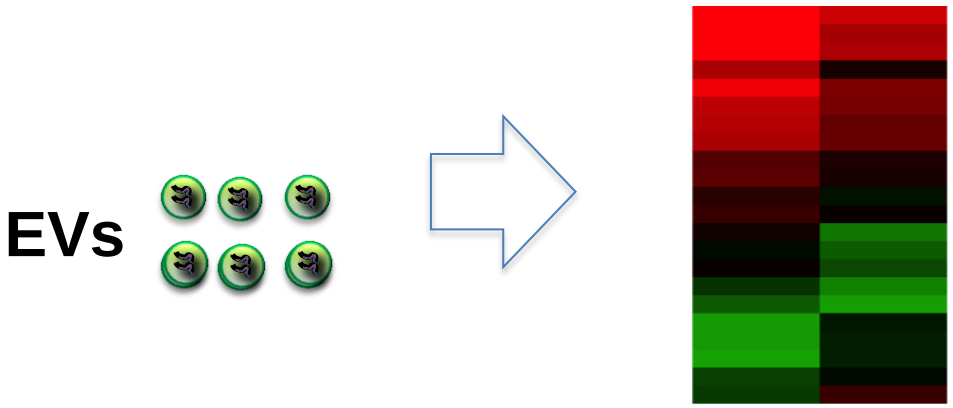
Methods



CSE: Cigarette smoke extract

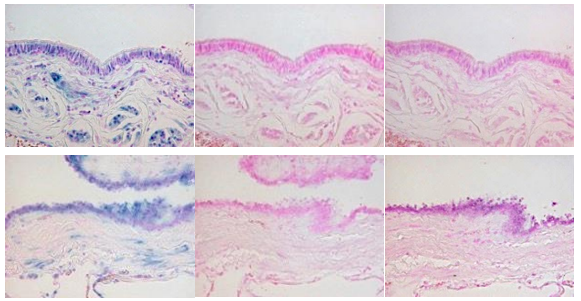
Ultracentrifuge
BECKMAN COURTER
SW 41Ti 35,000 rpm
(>100,000 x g)
70 min 4°C

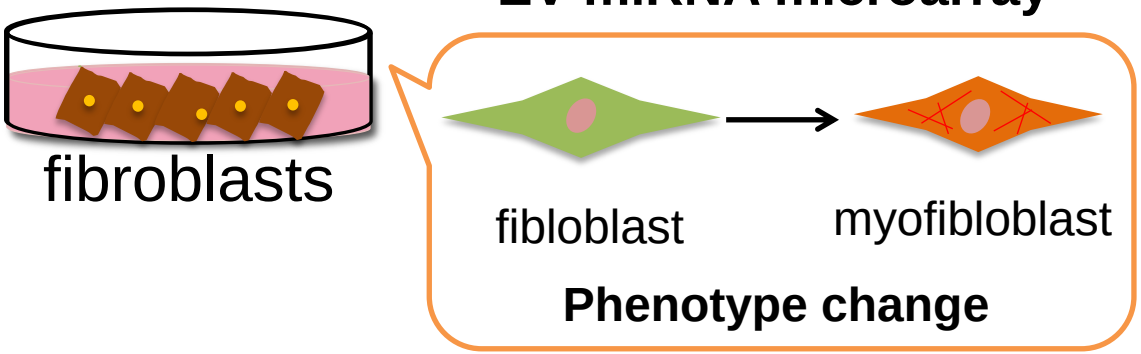
J Extracell Vesicles. 2013 May 27;2.



EV miRNA microarray

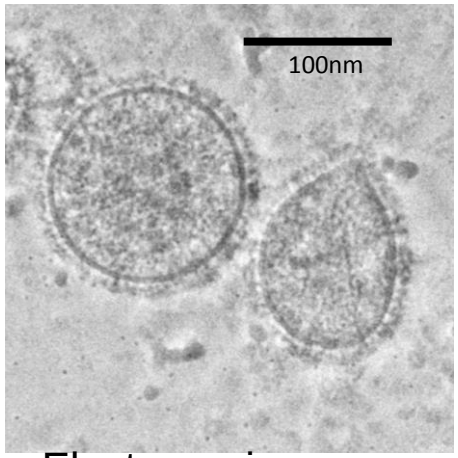
Using clinical samples





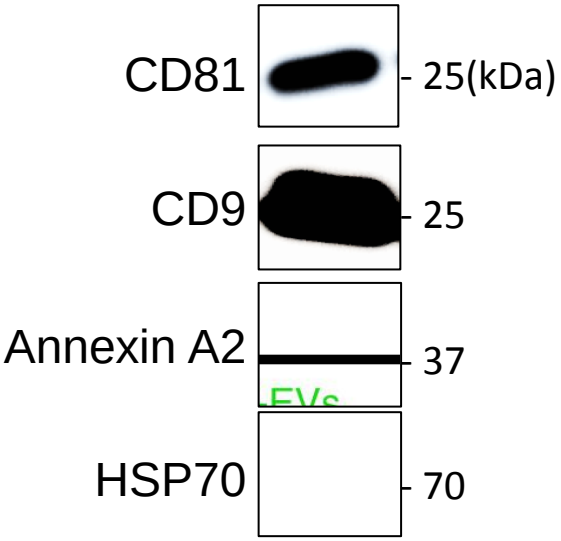
Characteristics of EVs from Human Bronchial Epithelial Cells

Bronchial epithelial cell



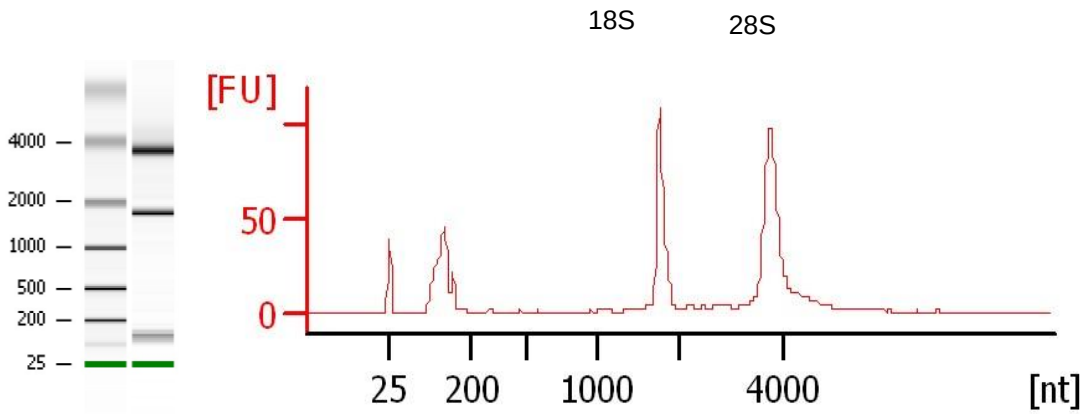
Electron microscopy

HBEC-EVs

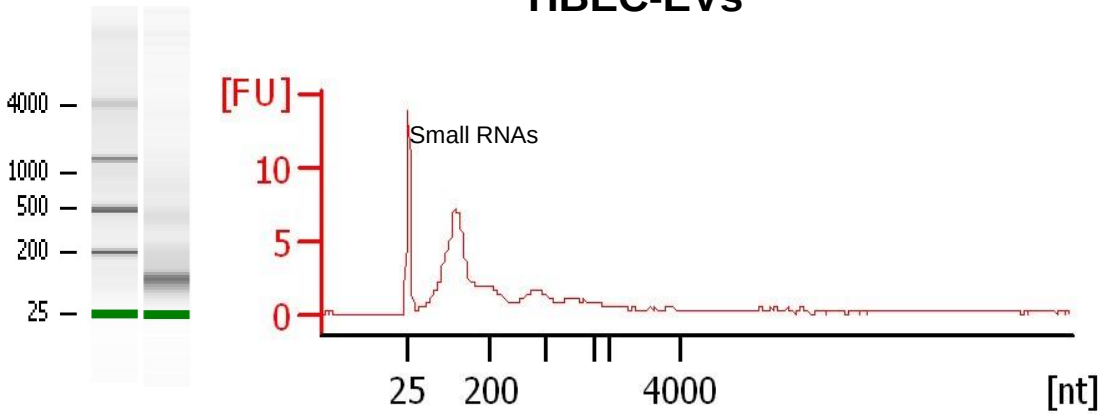


Bioanalyzer profile

HBEC

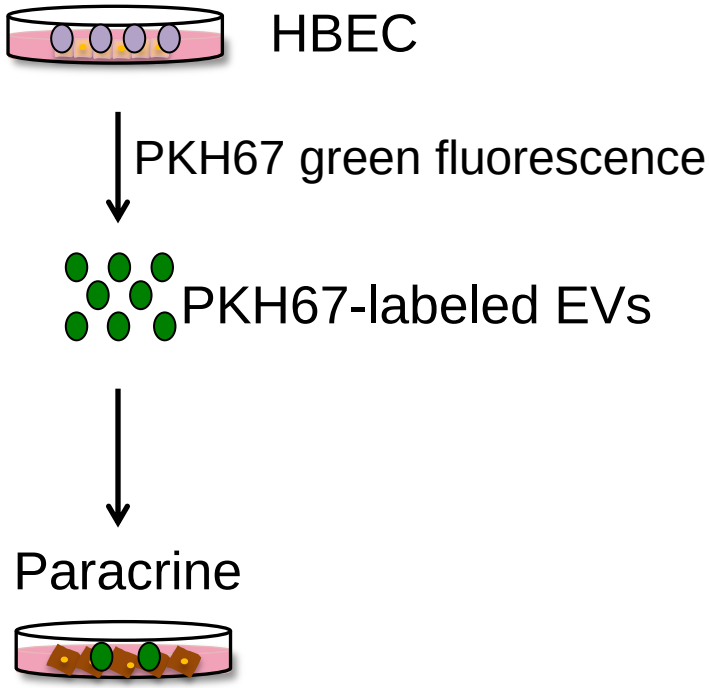


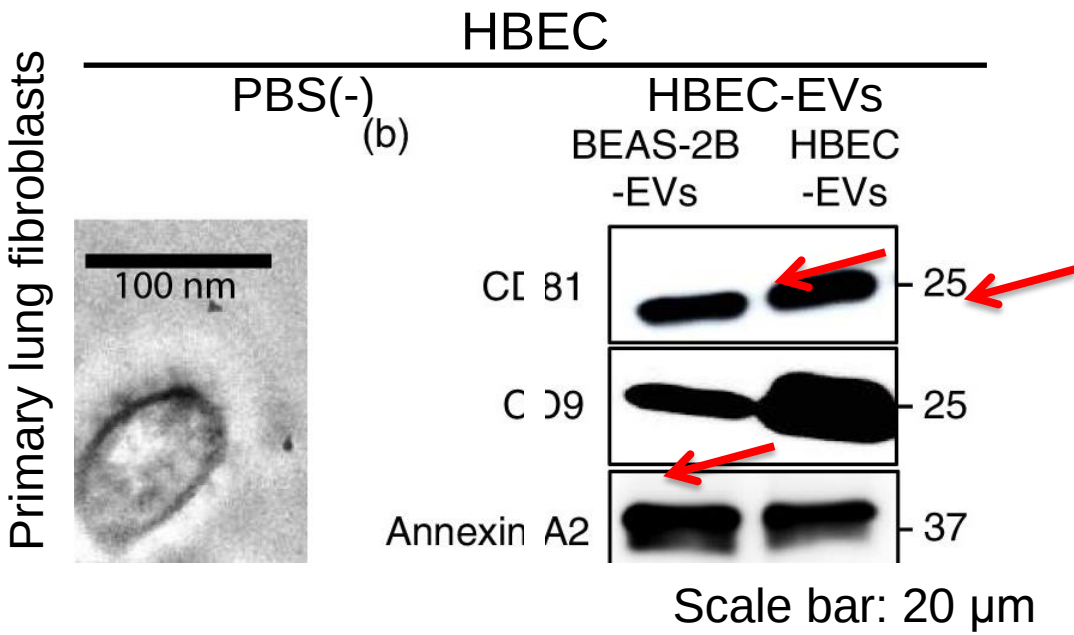
HBEC-EVs



Yu Fujita et al. JEV. 2015:10.3402/jev.v4.28388.

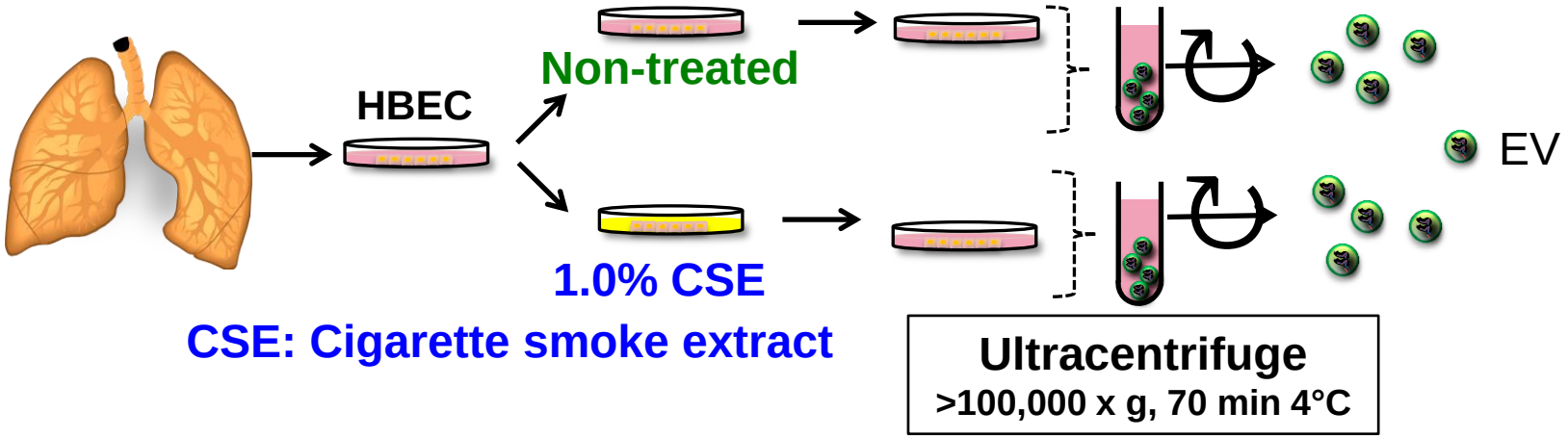
The Uptake of Bronchial Epithelial Cell-Derived EVs into Fibroblasts





Yu Fujita et al. JEV. 2015:10.3402/jev.v4.28388.

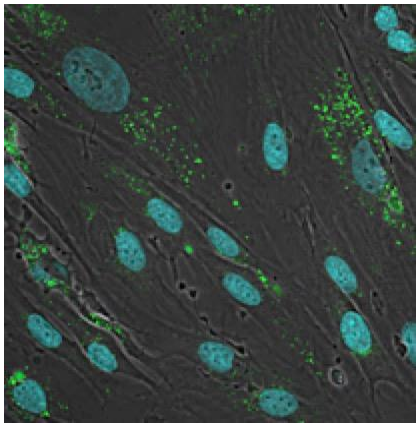
CSE-induced HBEC-EVs Accelerate Myofibroblast Differentiation in Airway Fibroblasts



Non-treated HBEC-EVs

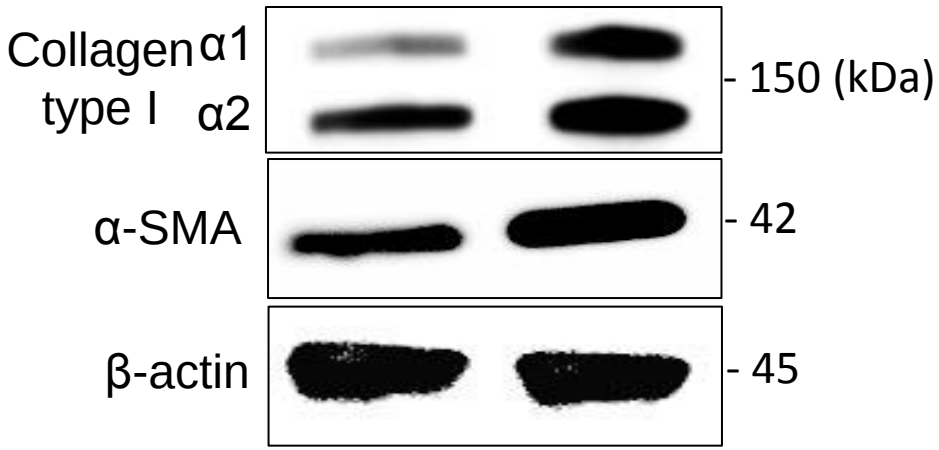
CSE-induced HBEC-EVs

Primary lung fibroblasts



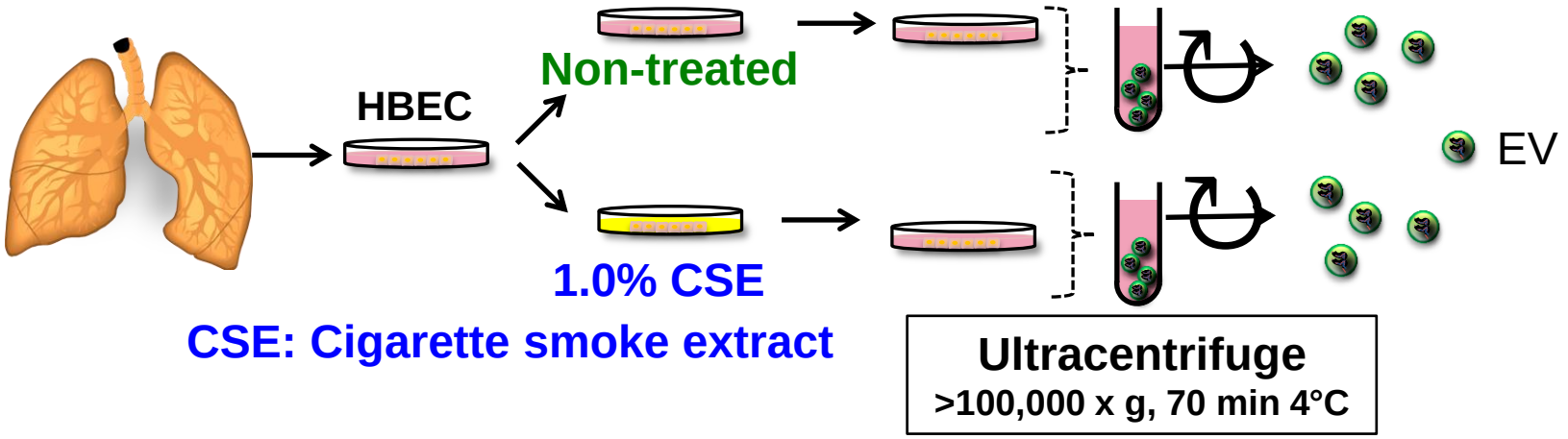
Primary lung fibroblasts

Non-treated HBEC-EVs | CSE-induced HBEC-EVs

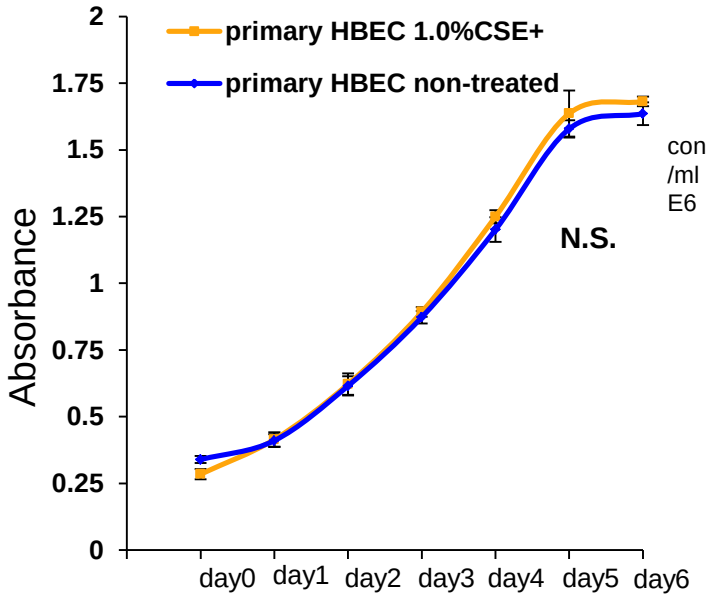


Yu Fujita et al. JEV. 2015:10.3402/jev.v4.28388.

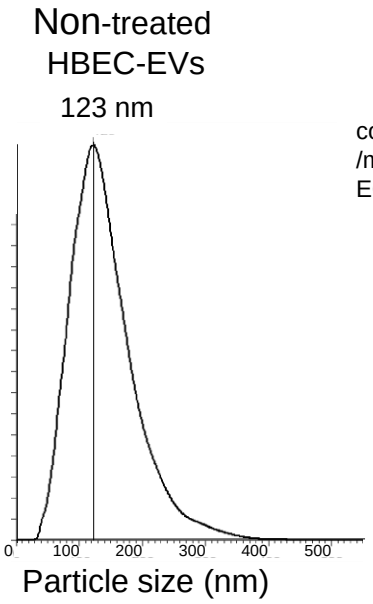
Cigarette Smoking Extract-induced HBEC-EVs

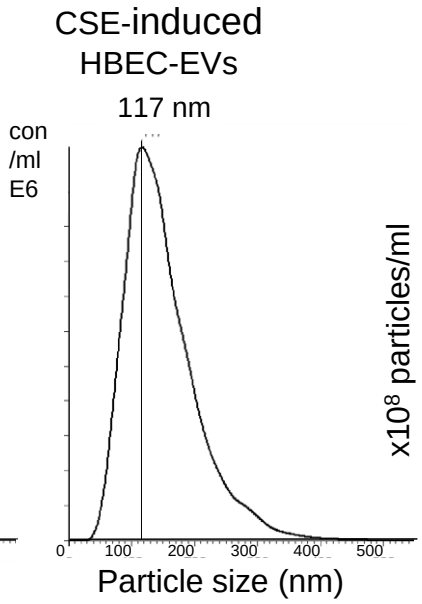


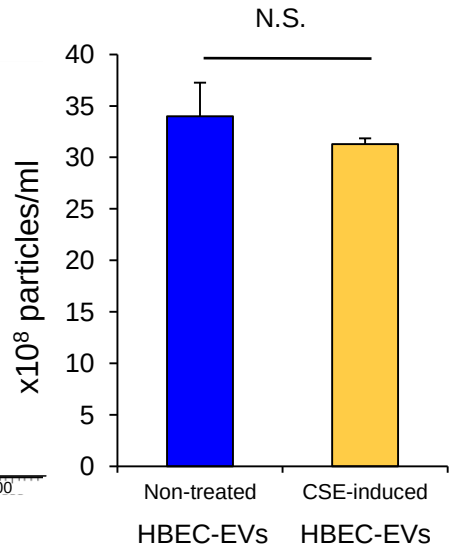
Cell proliferation assay



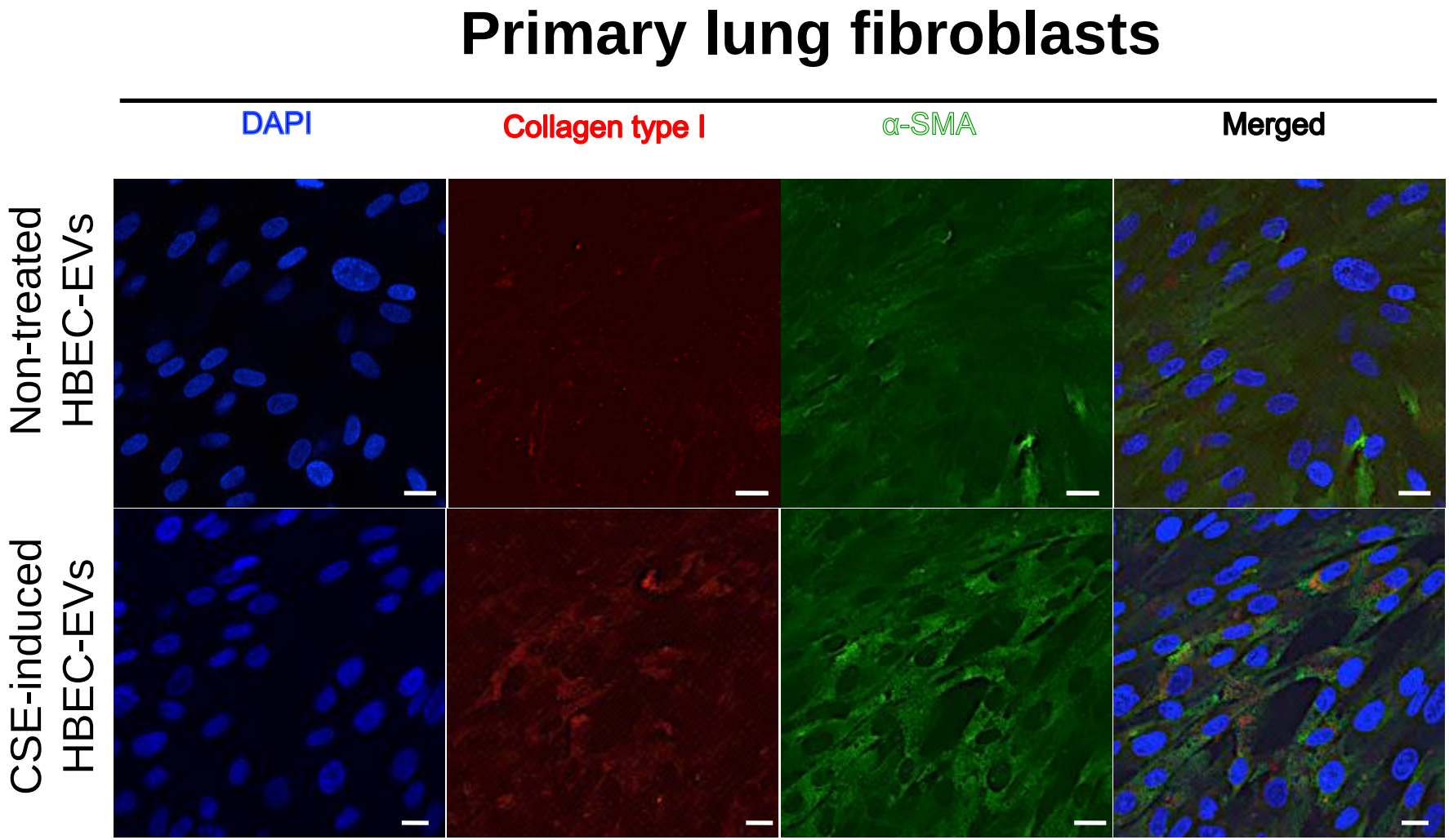
The size and count of EVs







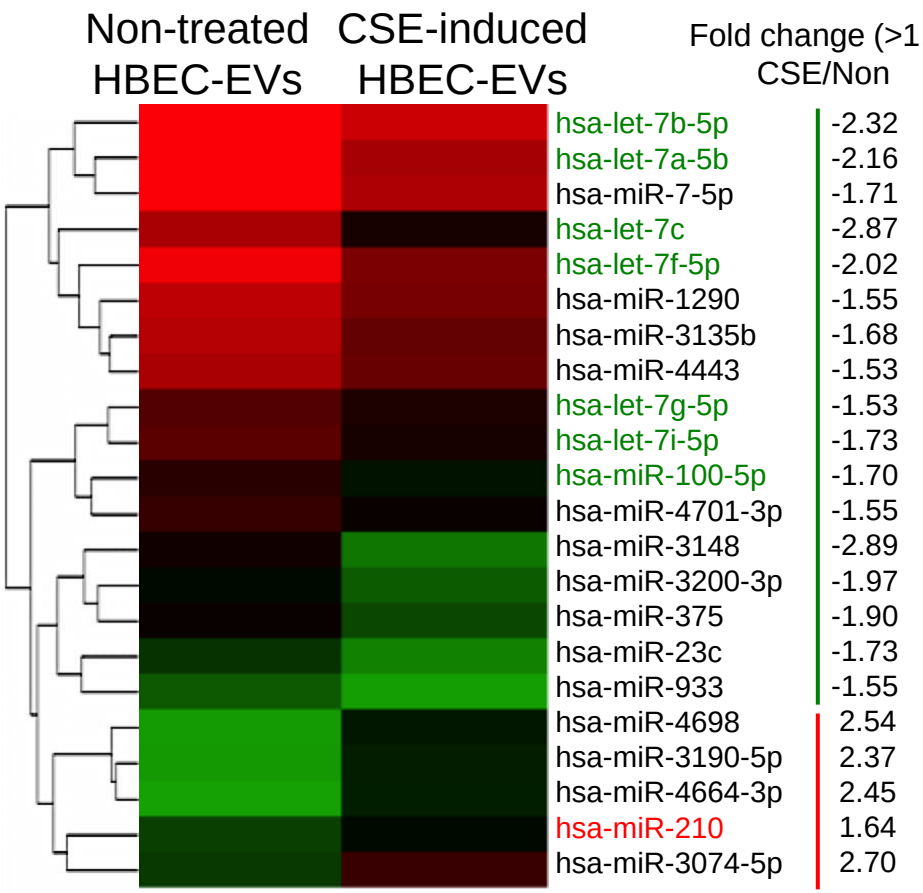
CSE-induced HBEC-EVs Accelerate Myofibroblast Differentiation in Airway Fibroblasts



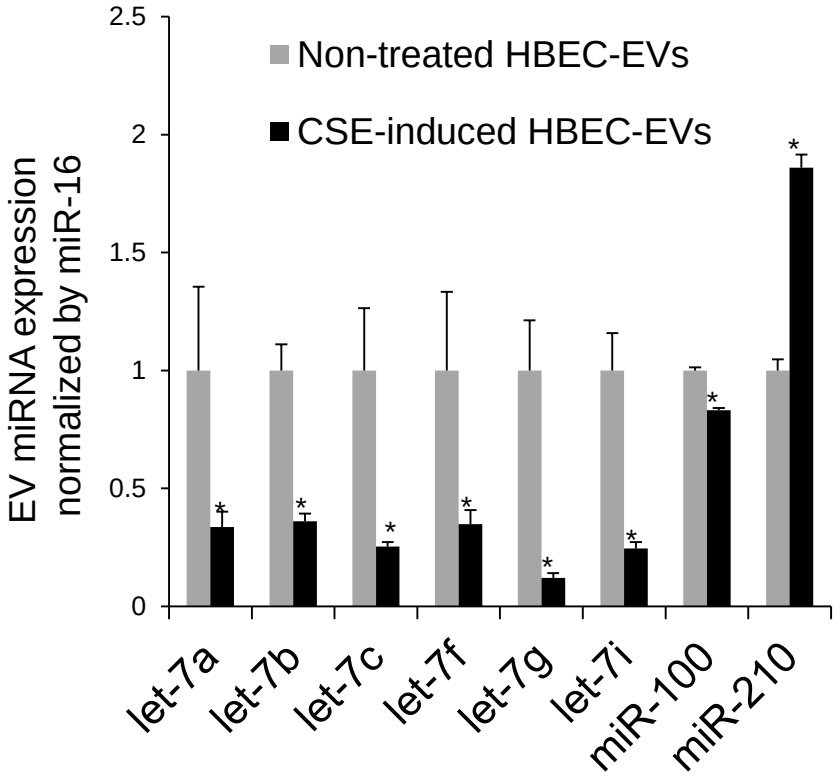
Yu Fujita et al. JEV. 2015:10.3402/jev.v4.28388.

Differential miRNA Expression in EV-derived from CSE-stimulated HBEC

Heatmap of the EV miRNA microarray

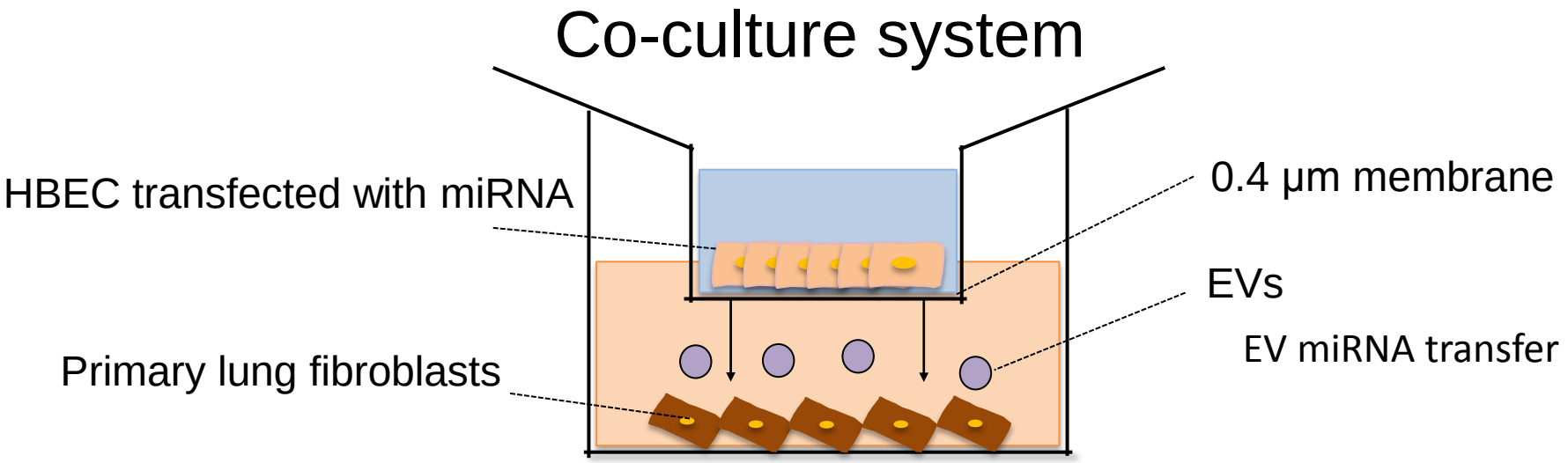


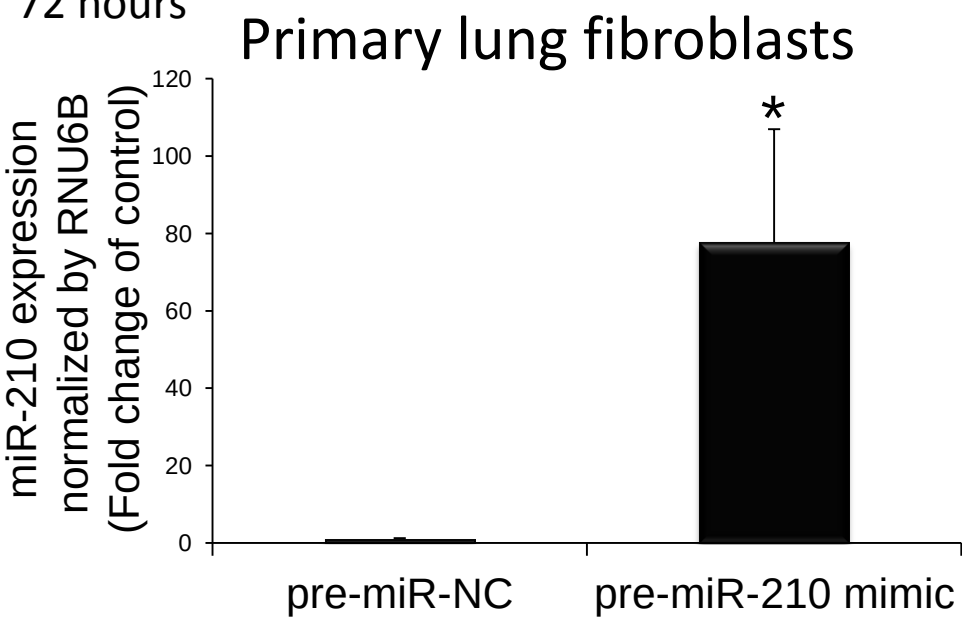
qRT-PCR validation

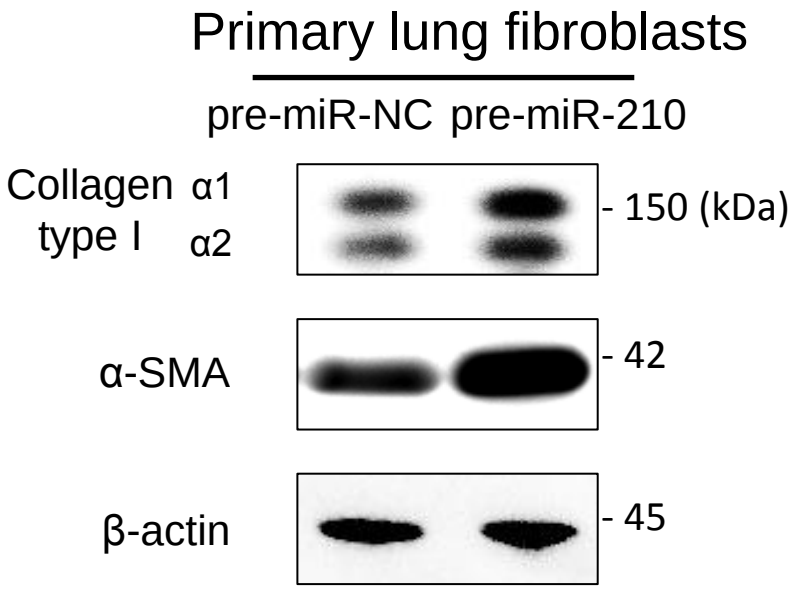


Yu Fujita et al. JEV. 2015:10.3402/jev.v4.28388.

EV miR-210 Is Transferred to Lung Fibroblasts and Promotes Myofibroblast Differentiation







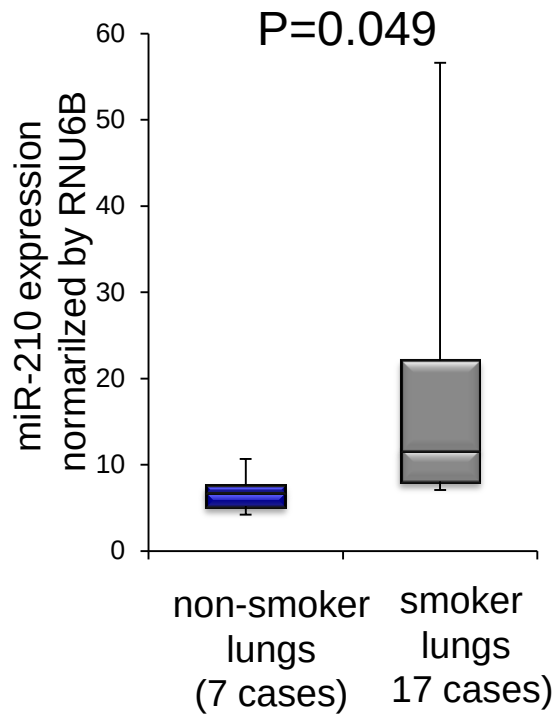
Yu Fujita et al. JEV. 2015:10.3402/jev.v4.28388.

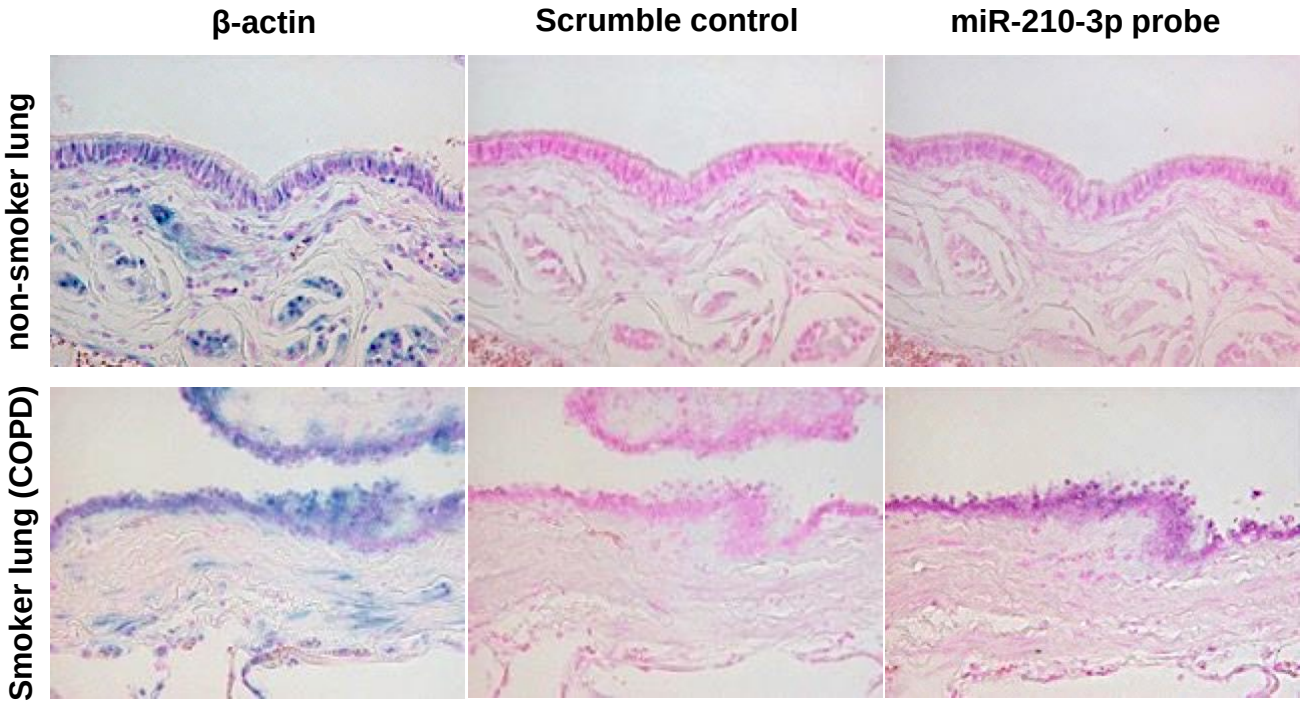
Increased miR-210 Expression in Smoker Lung

Characteristics of participating patients (for lung tissue)

	Non-smoker group	Smoker group	
		Non-COPD	COPD
	(*n* = 7)	(*n* = 13)	(*n* = 4)
Age, years	55.5 ± 8.6	60.8 ± 9.1	64.8 ± 5.1
Male, % of group	57.1	92.3	50.0
Brinkman Index	0	1100 ± 431.0	1305 ± 852.5
FEV1/FVC	83.4 ± 2.4	81.3 ± 7.1	63.0 ± 3.1

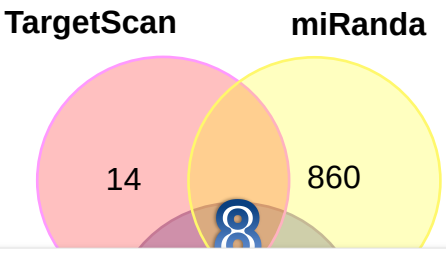
Abbreviations: COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity. Values are mean ± SD.

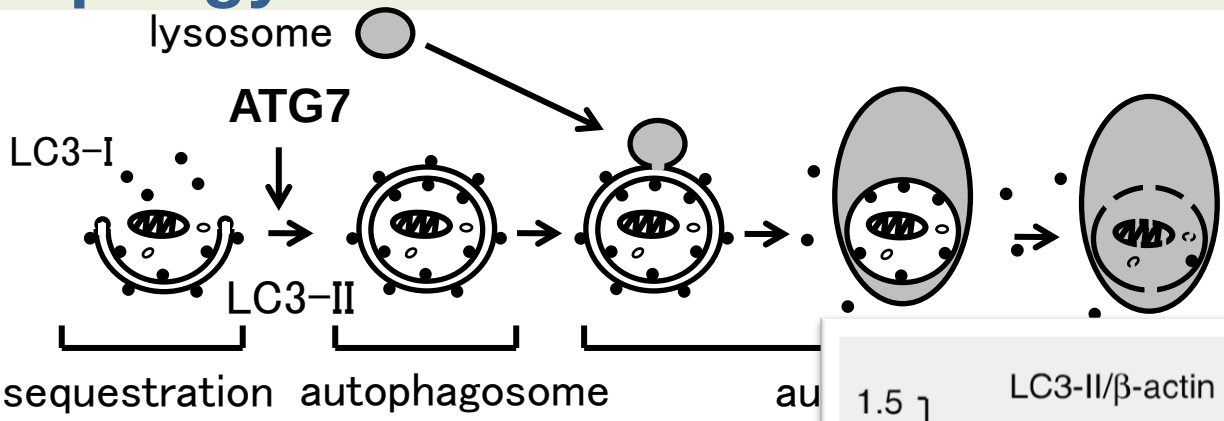


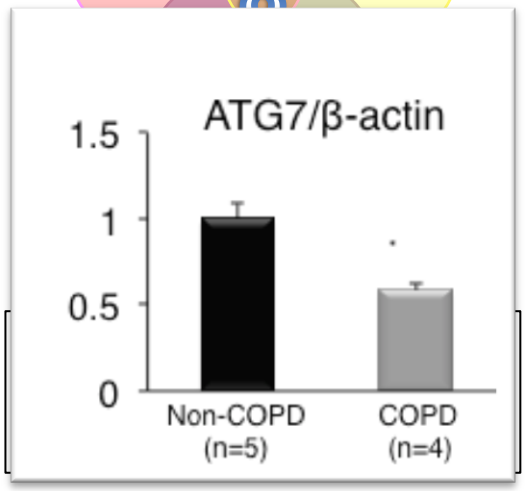


miR-210 Targets ATG7
Autophagy Related Gene

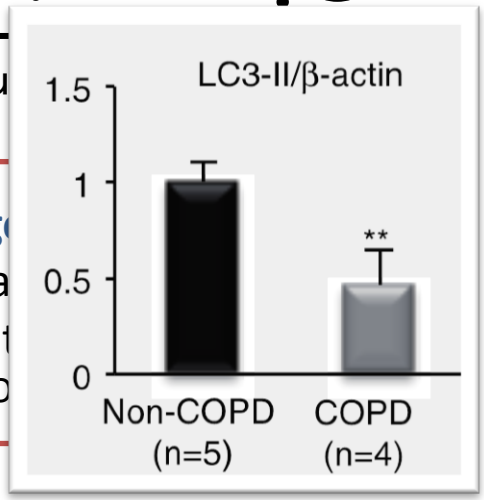
Target genes

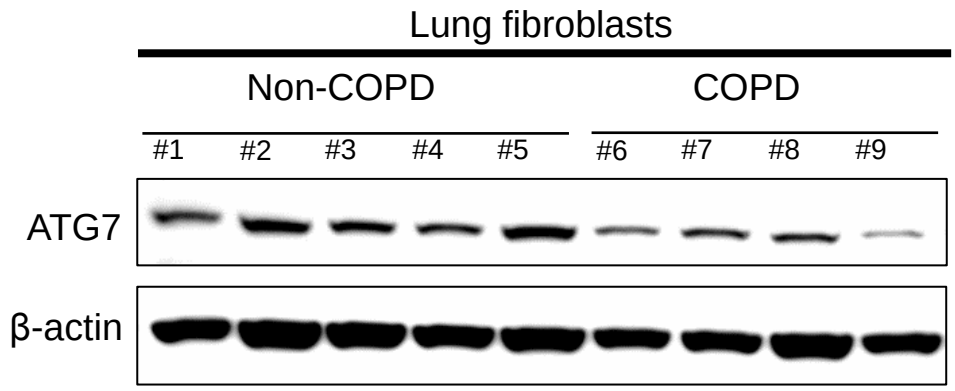


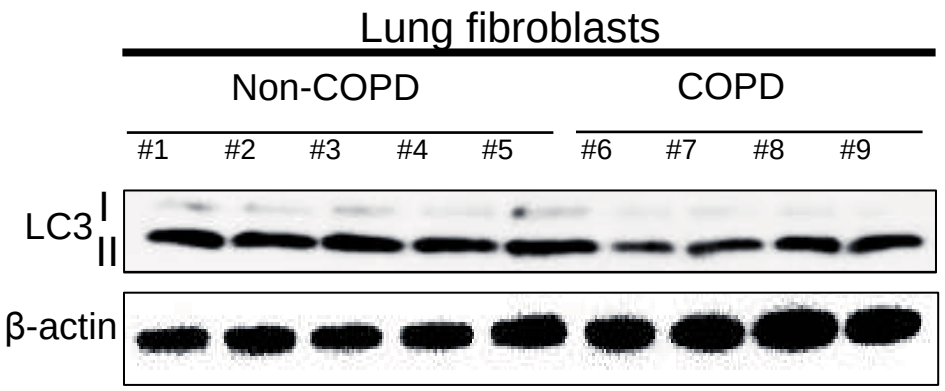




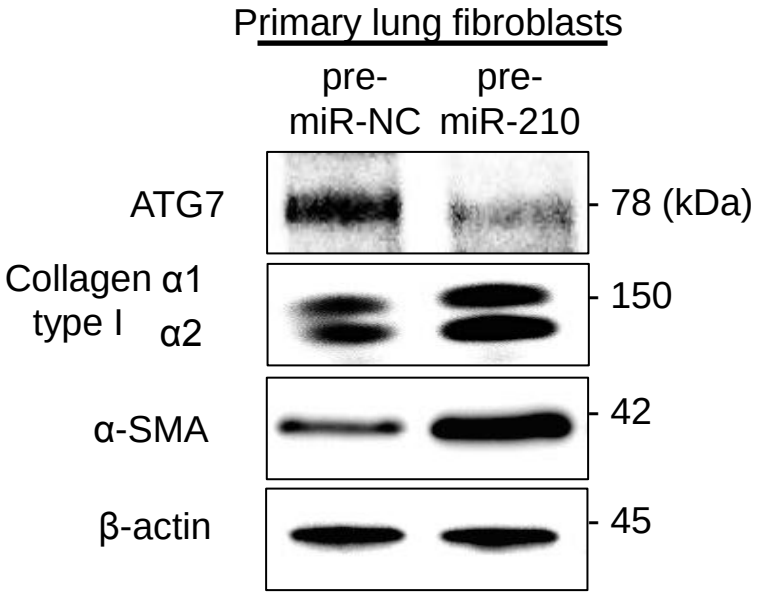
Autophagy plays a key role in the pathog
Insufficient autophagy promotes bronchia
senescence, which is involved in COPD pat
Araya J et al. C

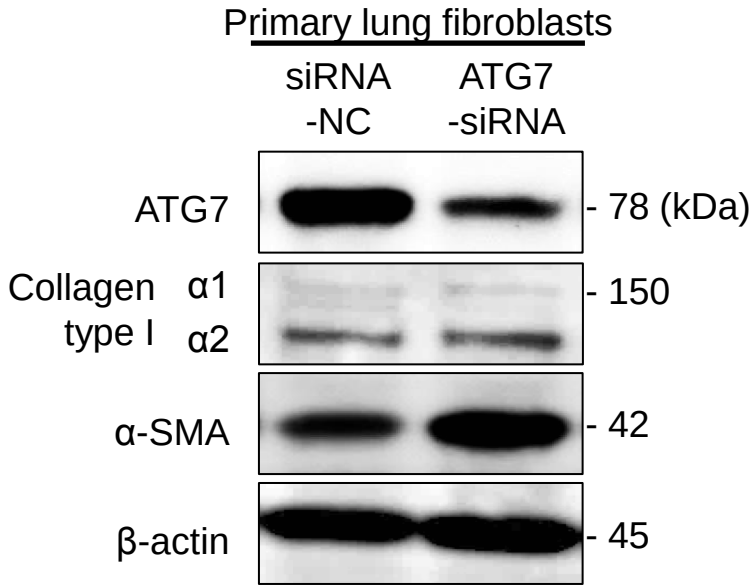




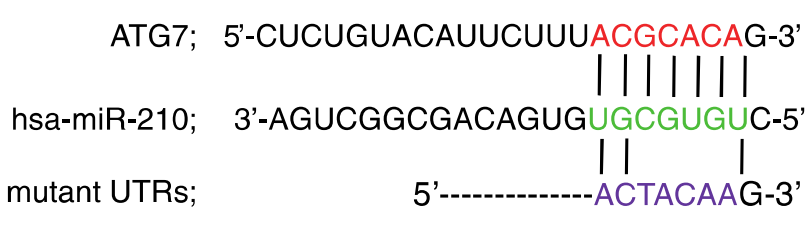


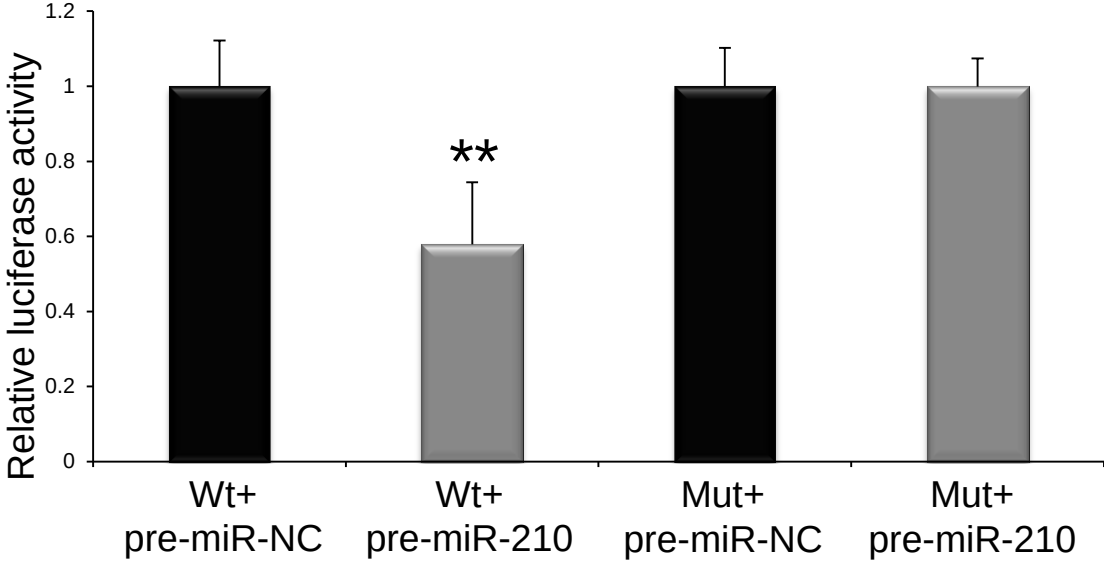
miR-210 Directly Regulates Autophagy Process via Targets ATG7 in Airway Fibroblasts



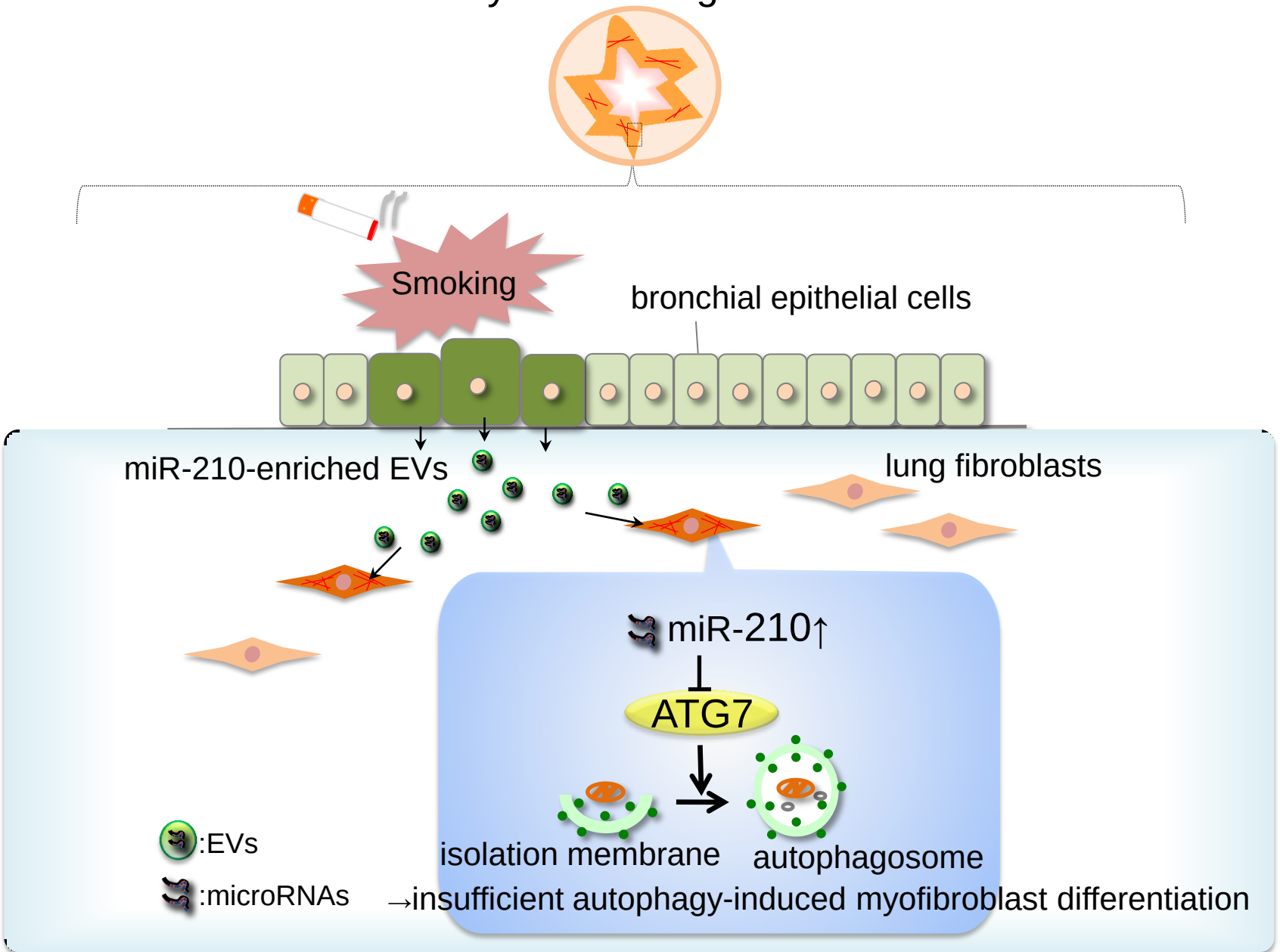


Reporter assay

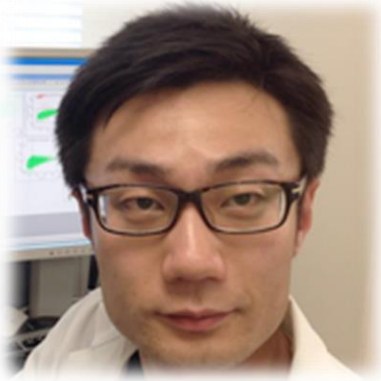




Summary


Airway remodeling in COPD
Smoking
bronchial epithelial cells
miR-210-enriched EVs
lung fibroblasts
miR-210↑
ATG7
isolation membrane
autophagosome
:EVs
:microRNAs
→insufficient autophagy-induced myofibroblast differentiation

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