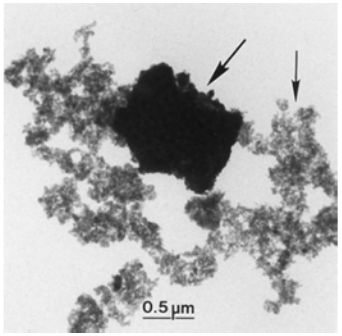
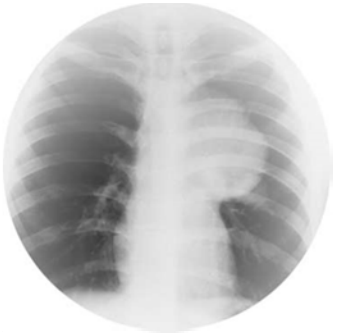
folkehelseinstituttet

The link between air pollution particles and lung cancer: mechanistic considerations





Er luftforurensing en relevant årsak til lungekreft?

Jørn A Holme

Editorial, thelancet: 388, August 6, 2016:

Lung cancer: despite advances, prevention is still best

Worldwide:
No 1 - 1·8 million diagnosed – No 1 of all cancer deaths

Norway :
No 2 - 3080 diagnosed (~10%) – No 1 of all cancer deaths (~20%)

Three main types of lung cancer

Non-small cell lung cancer (NSCLC; 80% to 85%)
– several subtypes (Squamous cell carcinoma, adenocarcinoma, and large cell carcinoma)

Small cell lung cancer (SCLC; 10% to 15%)

Lung Carcinoid Tumors (5%)

Various main type often different prognoses and treatment

Risk factors includes

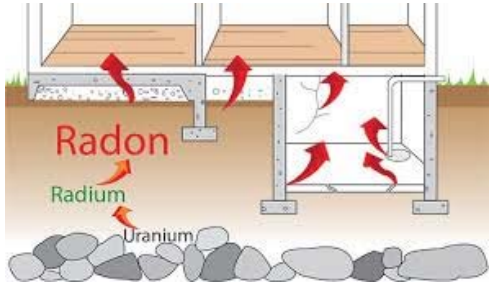
Genetic predisposition
Increased age
Environmental factors like cigarette smoke and air pollution – **preventable**

Male incidence rates stabilized/ Female still increasing:
Relative increases in adenocarcinomas and decreases in squamous-cell carcinoma

Environmental risk factor for lung cancer

Cigarette smoke (80%, complex mixture of chemical compounds bound to aerosol particles and/or are free in the gas phase)

Radon – bound to particles



Air pollution and diesel exhaust particles

complex mixture of various particular matter (PM) and gas

Workplace asbestos, or certain other chemicals

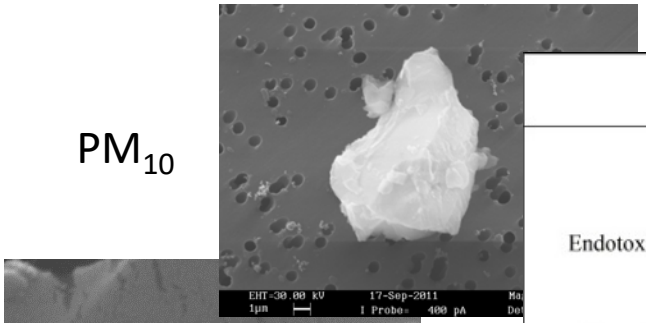
Airborne particular matter (PM)

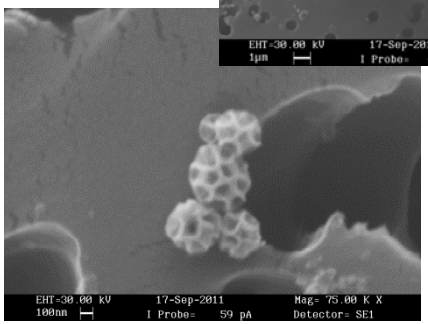
Ambient air PM composition is complex

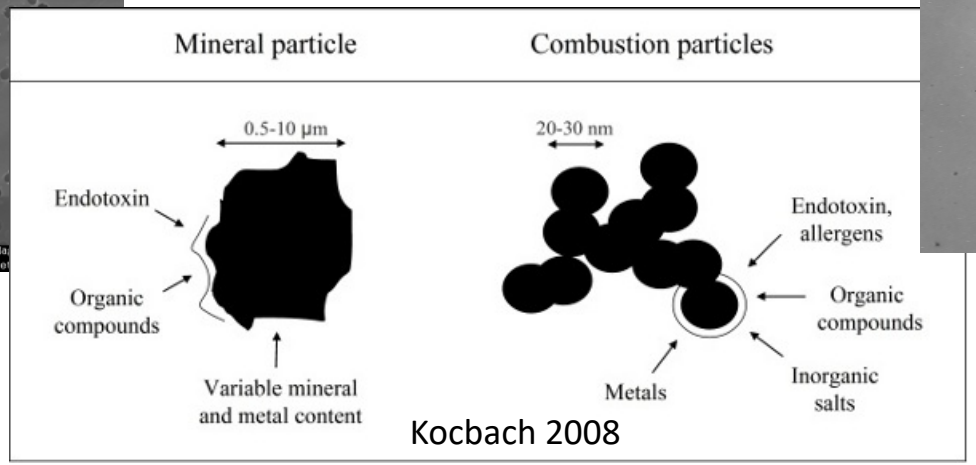
coarse (2.5-10 µm)
fine (<2.5 µm)
ultrafine (UFP <100 nm)

PM_{10} (coarse, fine and UFP)
$PM_{2.5}$ (fine and UFP)
UFP

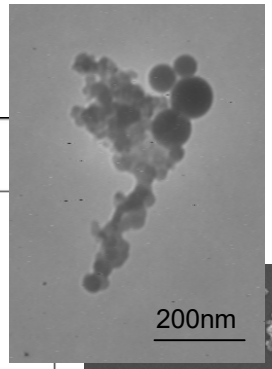
PM_{10}



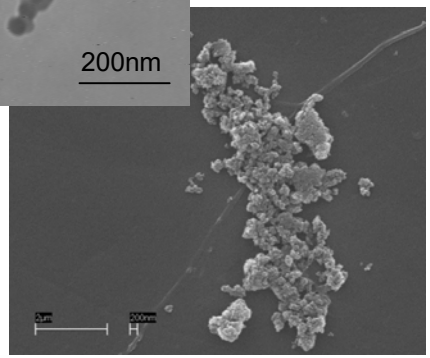




Kocbach 2008



$PM_{2.5}$



Sources:
- Fine and UFP: combustion processes (e.g. traffic, heating)
- Coarse: dust stirred up by vehicles on roads, biological

Deposition varies depending on size distribution and particle morphology

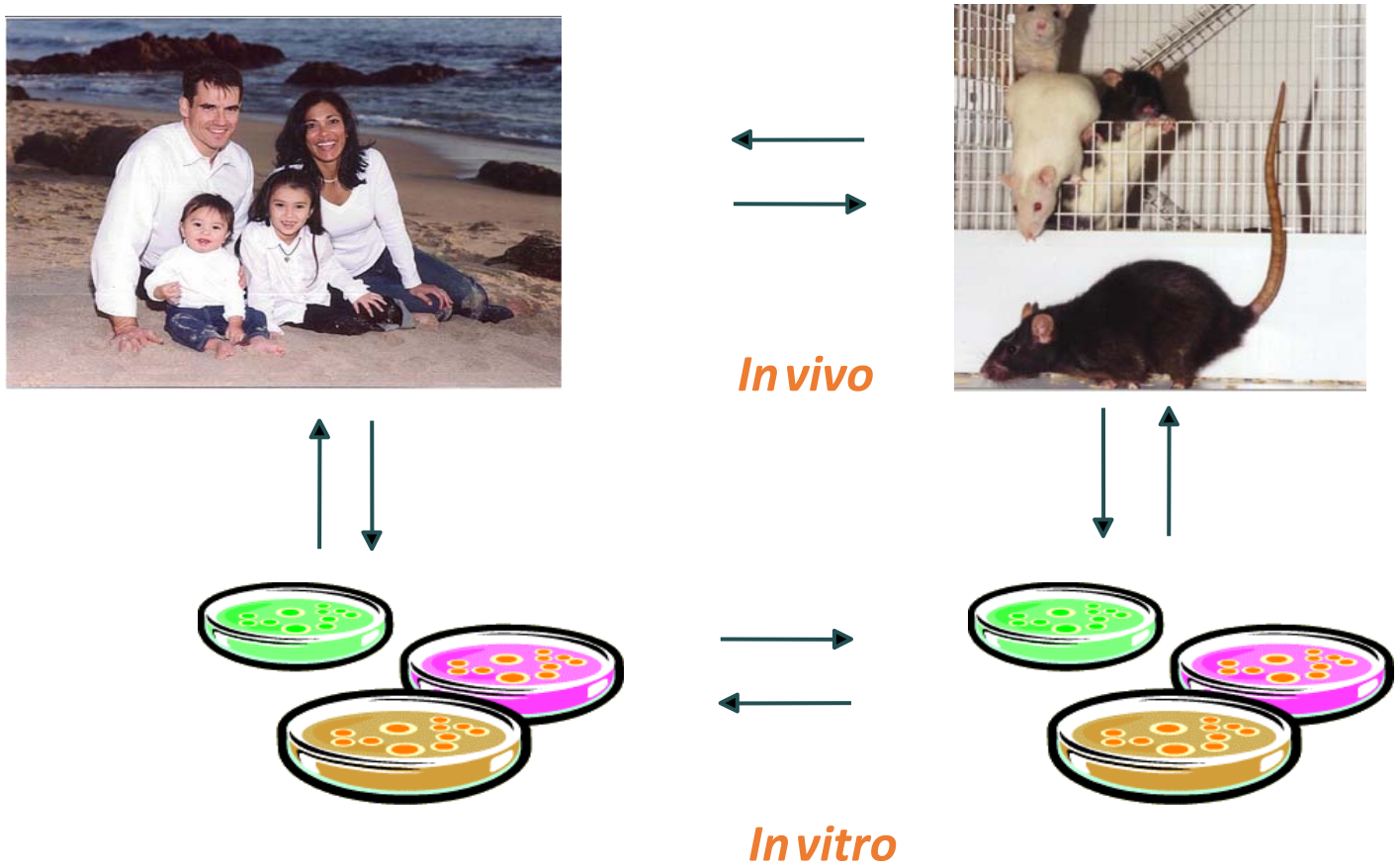
Outdoor air pollution and particular matter (PM):
cardiovascular diseases, chronic respiratory diseases and lung cancers

Sources:
road dust and combustion of diesel, wood, coal, biomass, and crude oil

Outdoor air pollution, outdoor air PM and diesel PM:
classified as carcinogenic to human beings by WHO – (IARC, SCI PUB NO. 161 - 2013)

IARC Group 1 carcinogen based on:

i) sufficient evidence of carcinogenicity in humans
ii) experimental animals
iii) strong mechanistic evidence



IARC, The Lancet, Oncology, 14, (13): 1262–1263, 2013

Air pollution and lung cancer incidence in 17 European cohorts: prospective analyses from the European Study of Cohorts for Air Pollution Effects (ESCAPE)

Hazard ratio (HR)

	Number of cohorts	HR (95% CI) for histological cancer subtype analysis		HR (95% CI) for standard analysis*	
		PM_{10}	$PM_{2.5}$	PM_{10}	$PM_{2.5}$
All participants					
All lung cancers	14†	1·22 (1·03–1·45)	1·18 (0·96–1·46)	1·22 (1·03–1·45)	1·18 (0·96–1·46)
Adenocarcinomas	11‡	1·51 (1·10–2·08)	1·55 (1·05–2·29)	1·22 (1·01–1·47)	1·16 (0·92–1·45)
Squamous-cell carcinomas	7§	0·84 (0·50–1·40)	1·46 (0·43–4·90)	1·19 (0·94–1·51)	1·18 (0·91–1·52)
Participants who did not change residence					
All lung cancers	10¶	1·48 (1·16–1·88)	1·33 (0·98–1·80)	1·22 (1·02–1·46)	1·20 (0·96–1·51)
Adenocarcinomas	8‖	2·27 (1·32–3·91)	1·65 (0·93–2·95)	1·19 (0·98–1·45)	1·17 (0·92–1·49)
Squamous-cell carcinomas	3**	0·64 (0·28–1·48)	0·65 (0·16–2·57)	1·21 (0·94–1·55)	1·22 (0·93–1·60)

Meta-analysis results based on confounder model 2. See appendix (p 25) for numbers of participants and lung cancer cases contributing to each meta-analysis result. HRs are per 10 μg/m³ of PM_{10} and per 5 μg/m³ of $PM_{2.5}$. HR=hazard ratio. PM_{10}=particulate matter with diameter <10 μm. $PM_{2.5}$=particulate matter with diameter <2·5 μm. *Standard analysis, disregarding histological cancer subtype (ie, with all lung cancers as the endpoint and including all participants in the same cohorts as used in the histological cancer subtype analysis). †HUBRO, SNAC-K, SALT, Sixty, SDPP, DCH, EPIC-MORGEN, EPIC-PROSPECT, EPIC-Oxford, VHM&PP, EPIC-Turin, SIDRIA-Turin, SIDRIA-Rome, EPIC-Athens. ‡HUBRO, SALT, Sixty, SDPP, DCH, EPIC-MORGEN, EPIC-PROSPECT, EPIC-Oxford, VHM&PP, EPIC-Turin, EPIC-Athens. §Sixty, SDPP, DCH, EPIC-MORGEN, EPIC-PROSPECT, EPIC-Oxford, VHM&PP. ¶HUBRO, SNAC-K, SALT, Sixty, SDPP, DCH, VHM&PP, SIDRIA-Turin, SIDRIA-Rome, EPIC-Athens. ‖HUBRO, SNAC-K, SALT, Sixty, SDPP, DCH, VHM&PP, EPIC-Athens. **Sixty, DCH, VHM&PP.

Table 3: Associations between PM_{10} and $PM_{2.5}$ and risk for lung cancer for all participants and those who did not change residence during follow-up, according to histological cancer subtype

Raaschou-Nielsen O et al., Lancet Oncol. 2013;14(9):813-22

Hazard ratio (HR) at different exposure levels

- association is stronger for non-smokers and people with low fruit intake

Figure 1: **Areas where cohort members lived, measurements were taken, and land-use regression models for prediction of air pollution were developed**
NO_2=nitrogen dioxide. NOx=nitrogen oxides (the sum of nitric oxide and nitrogen dioxide). PM=particulate matter.

	Number of cohorts	HR (95% CI) for threshold analyses	HR (95% CI) for standard analyses†
PM_{10}			
15 µg/m³	5‡	1·34 (0·51–3·52)	1·21 (0·87–1·68)
20 µg/m³	8§	1·31 (0·94–1·82)	1·13 (0·92–1·40)
25 µg/m³	10¶	1·17 (0·93–1·47)	1·12 (0·91–1·38)
30 µg/m³	10¶	1·13 (0·92–1·40)	1·12 (0·91–1·38)
35 µg/m³	11‖	1·11 (0·90–1·37)	1·15 (0·95–1·39)
40 µg/m³	12**	1·13 (0·92–1·39)	1·17 (0·97–1·41)
No threshold	14 (all)††	1·22 (1·03–1·45)	1·22 (1·03–1·45)
$PM_{2·5}$			
10 µg/m³	6‡‡	1·20 (0·55–2·66)	0·97 (0·63–1·49)
15 µg/m³	8§§	1·11 (0·85–1·45)	1·15 (0·90–1·47)
20 µg/m³	11¶¶	1·14 (0·90–1·45)	1·16 (0·92–1·45)
25 µg/m³	11¶¶	1·13 (0·90–1·43)	1·16 (0·92–1·45)
No threshold	14 (all)††	1·18 (0·96–1·46)	1·18 (0·96–1·46)

Meta-analysis results based on confounder model 3, see appendix (p 25) for numbers of participants and lung cancer cases contributing to each meta-analysis result. HRs are per 10 µg/m³ of PM_{10} and per 5 µg/m³ of $PM_{2·5}$. HR=hazard ratio. PM_{10}=particulate matter with diameter <10 µm. $PM_{2·5}$=particulate matter with diameter <2·5 µm. †Participants living at addresses (at baseline) with air pollution above these thresholds were excluded from the analysis. †Standard analysis, disregarding thresholds (ie, including all participants in the same cohorts as used in the threshold analysis). ‡HUBRO, Sixty, SDPP, DCH, EPIC-Oxford. §HUBRO, SNAC-K, SALT, Sixty, SDPP, DCH, EPIC-Oxford, VHM&PP. ¶HUBRO, SNAC-K, SALT, Sixty, SDPP, DCH, EPIC-MORGEN, EPIC-PROSPECT, EPIC-Oxford, VHM&PP. ‖HUBRO, SNAC-K, SALT, Sixty, SDPP, DCH, EPIC-MORGEN, EPIC-PROSPECT, EPIC-Oxford, VHM&PP, SIDRIA-Rome. **HUBRO, SNAC-K, SALT, Sixty, SDPP, DCH, EPIC-MORGEN, EPIC-PROSPECT, EPIC-Oxford, VHM&PP, EPIC-Turin, SIDRIA-Rome. ††HUBRO, SNAC-K, SALT, Sixty, SDPP, DCH, EPIC-MORGEN, EPIC-PROSPECT, EPIC-Oxford, VHM&PP, EPIC-Turin, SIDRIA-Turin, SIDRIA-Rome, EPIC-Athens. ‡‡SNAC-K, SALT, Sixty, SDPP, DCH, EPIC-Oxford. §§HUBRO, SNAC-K, SALT, Sixty, SDPP, DCH, EPIC-Oxford, VHM&PP. ¶¶HUBRO, SNAC-K, SALT, Sixty, SDPP, DCH, EPIC-MORGEN, EPIC-PROSPECT, EPIC-Oxford, VHM&PP, SIDRIA-Rome.

Table 4: **Associations between PM_{10} and $PM_{2·5}$ and risk for lung cancer, according to air pollution thresholds***

Raaschou-Nielsen O et al., Lancet Oncol. 2013;14(9):813-22

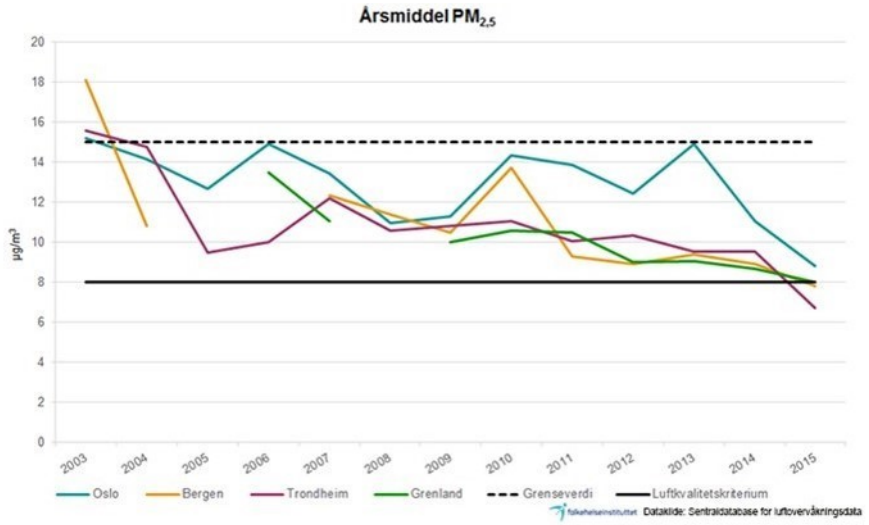
WHO in 2004:

smoking - 5·1 million deaths and 71% of lung cancer

air pollution - 1·2 million deaths and 8% of lung cancer

Levels of $PM_{2.5}$ and PM_{10} in Norway

A



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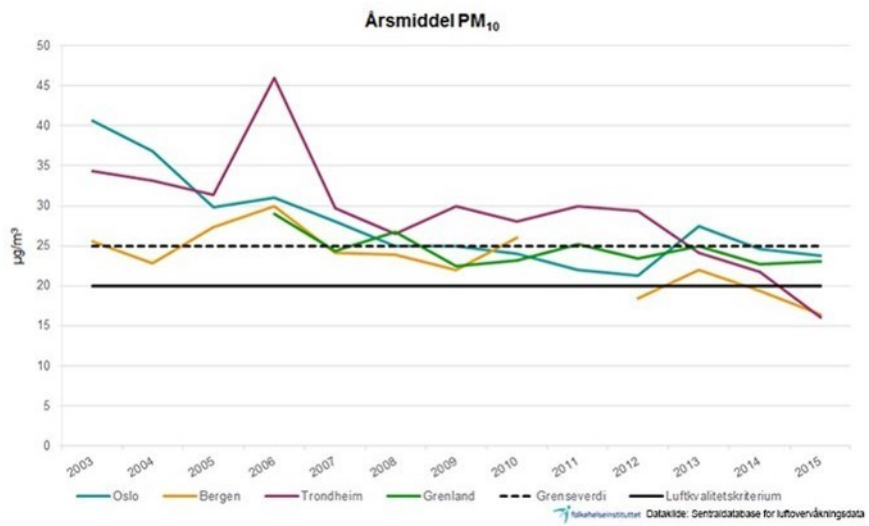
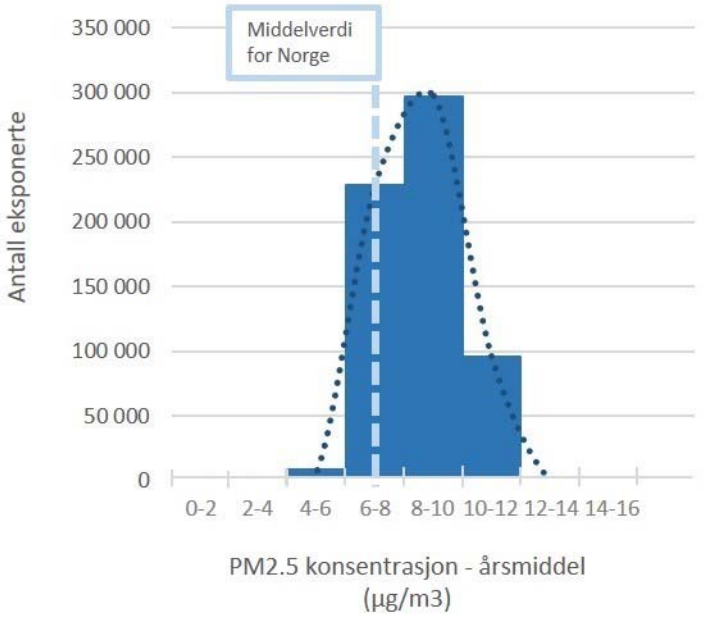
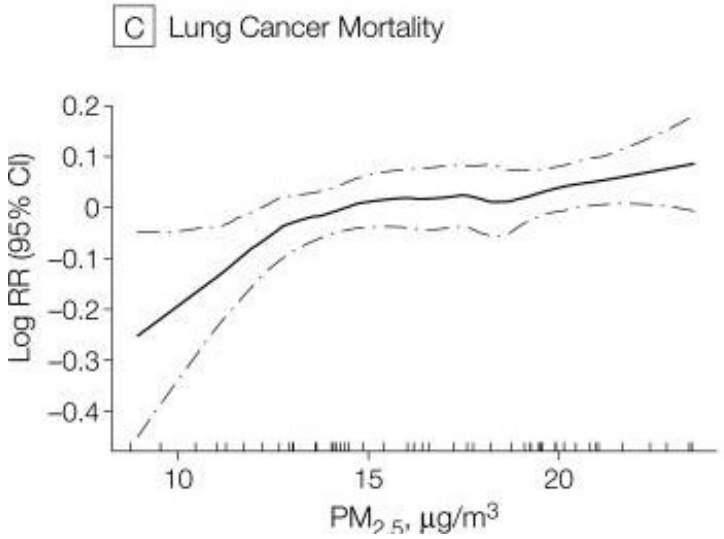


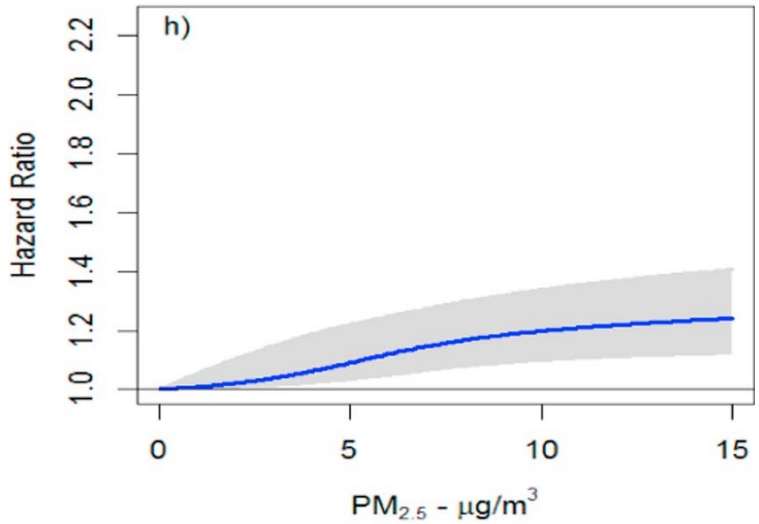
No apparent threshold



Mechanistisk understanding to support epidemiological studies are needed



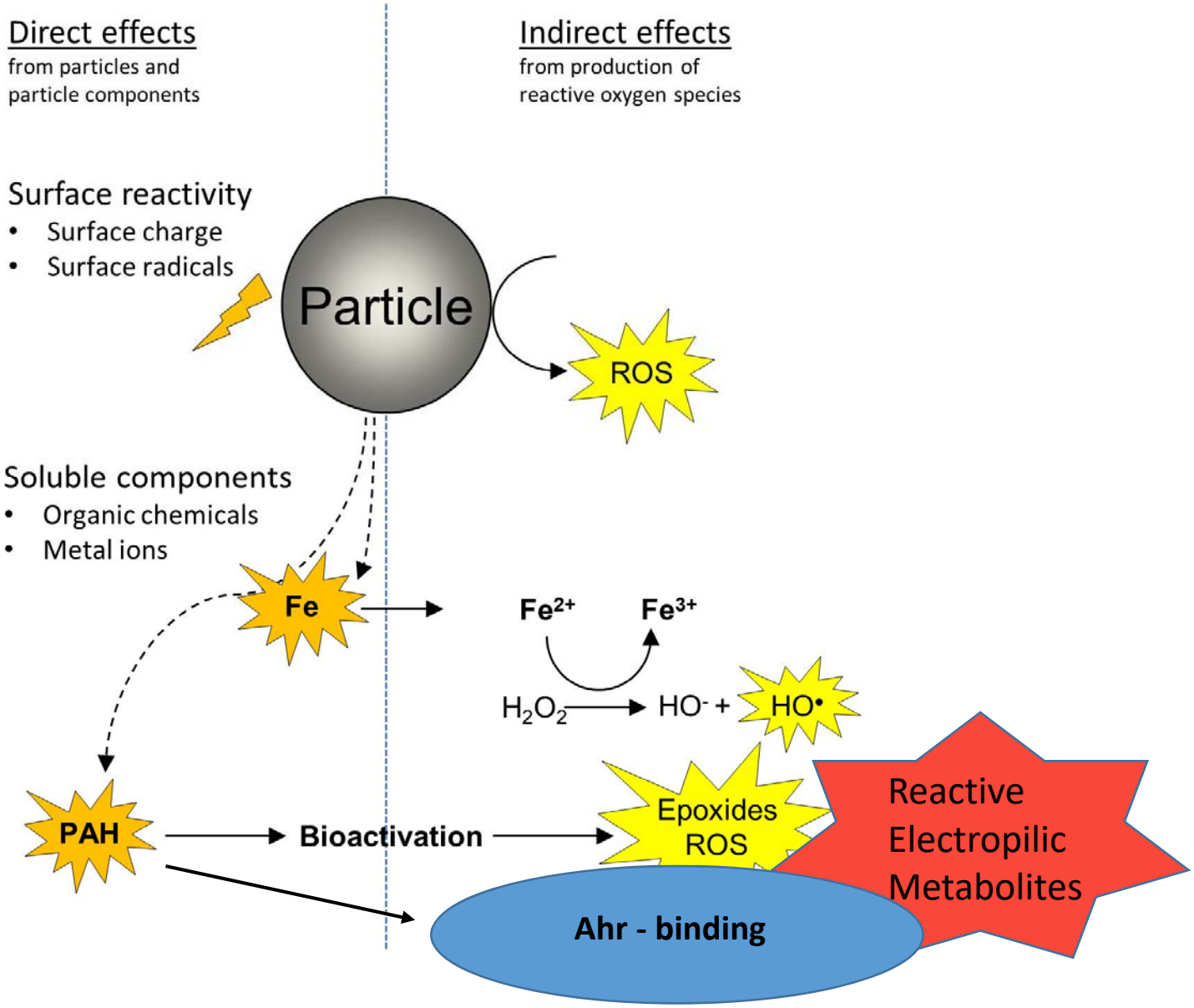
Pope CA 3rd et al JAMA, 2002



Pinault LL et al, Environ Res., 2017

PM properties related to cancer

PM as such as well as chemicals adsorbed (polycyclic aromatic hydrocarbons): reactive electrophilic metabolites, oxygen species, receptor binding



Effects of PM linked to: cancer initiation, promotion and micro-environment

Binding to various cellular receptors / ROS/REM reacting with macromolecules

DNA damage /DDR - Mutation

- ssDNAbreaks/ adducts
- Gene mutation
- Chromosomal aberrations/ SCE/MN – genetic instability

Cell death (apoptosis and/ or necrosis) – resistance towards cell death

Cell cycle alteration

Metabolic reprogramming

- increased glycolysis and upregulation of amino acid and lipid metabolism

Cellular interactions:

- tight junction
- gap junction (GJIC)
- contact inhibition – proliferation

Cell migration and invasion

Inflammatory responses

Extracellular matrix (ECM)

Epithelial-to-mesenchymal transition (EMT)

Cell transformation

Epigenetic changes

1.

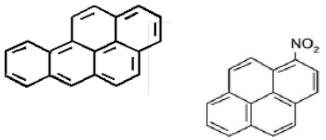
Mechanisms involved

USB and SB — **Early events** — ROS and REM

membrane / receptors/ channels /----------/ nucleophilic sites on proteins/ DNA

1.

Mechanisms involved

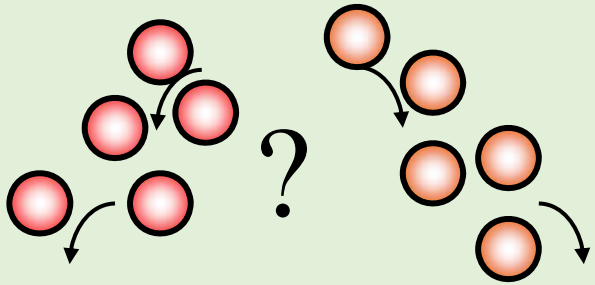


USB and SB — **Early events** — ROS and REM

membrane / receptors/ channels /----------/ nucleophilic sites on proteins/ DNA

2.

Cellular signalling



Ionic homeostasis

Phosphorylations

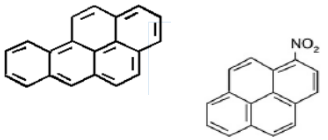
ROS

Translocation

Transcription

1.

Mechanisms involved



USB and SB — **Early events** — ROS and REM

membrane / receptors/ channels /----------/ nucleophilic sites on proteins/ DNA

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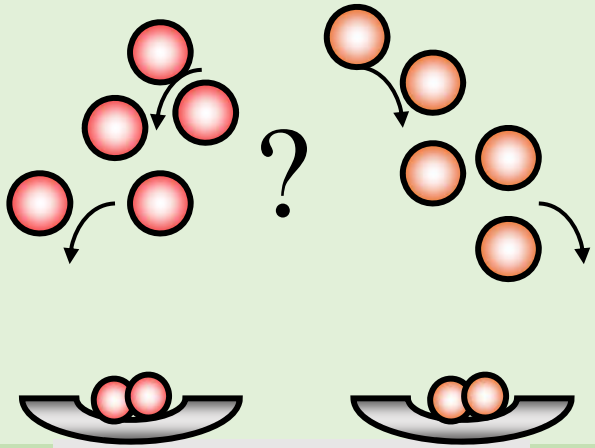

Ionic homeostasis

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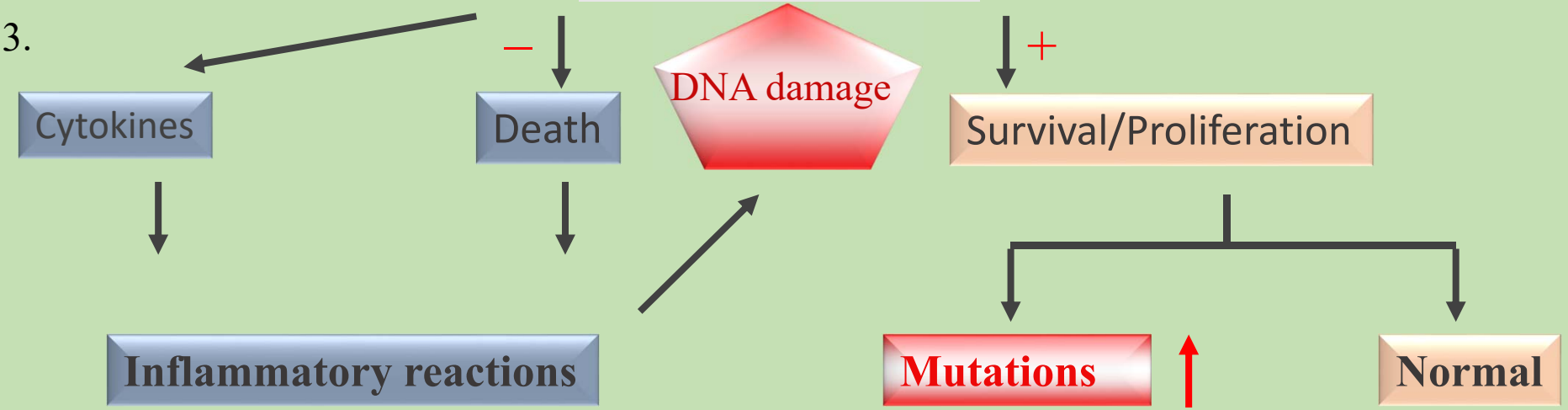
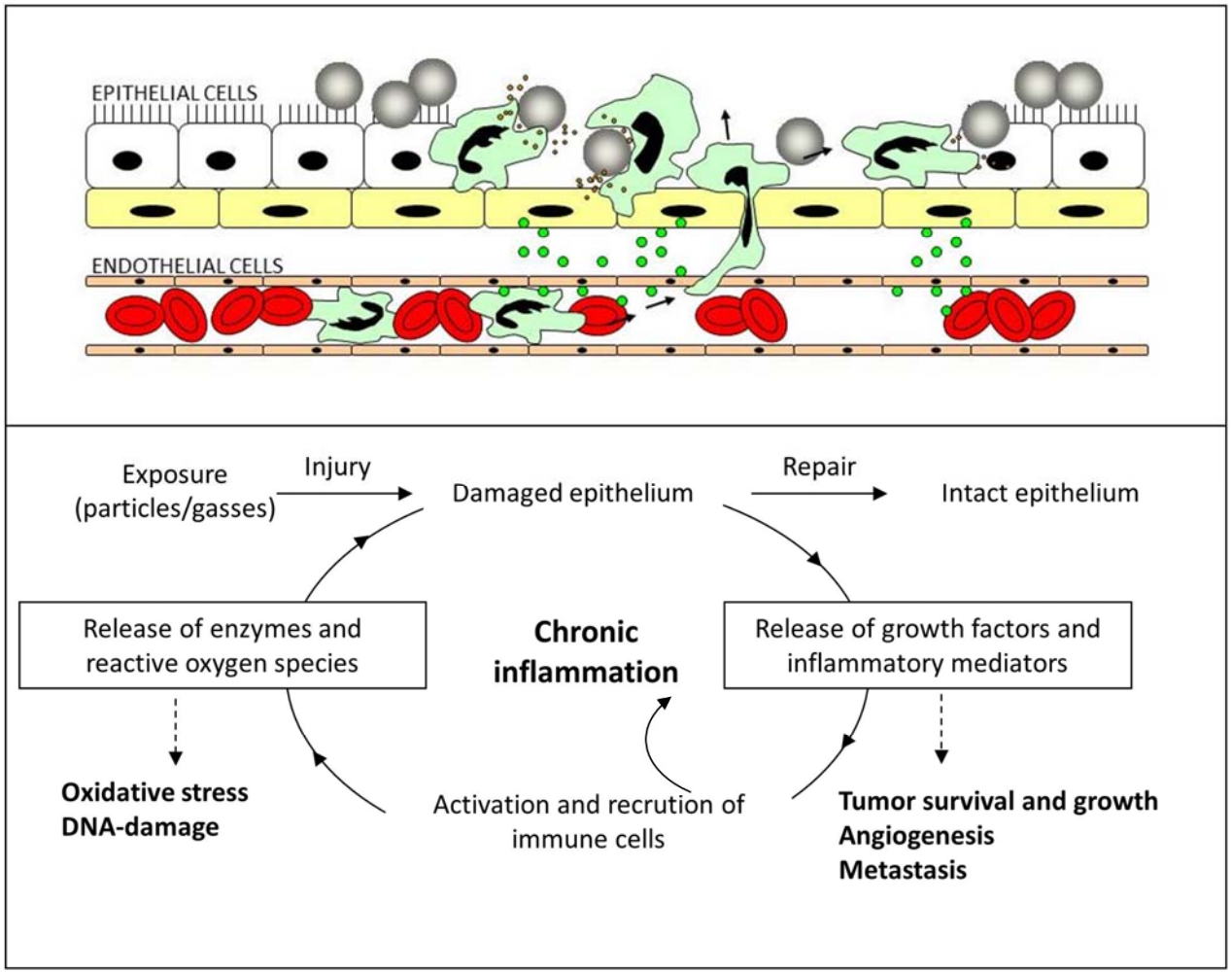


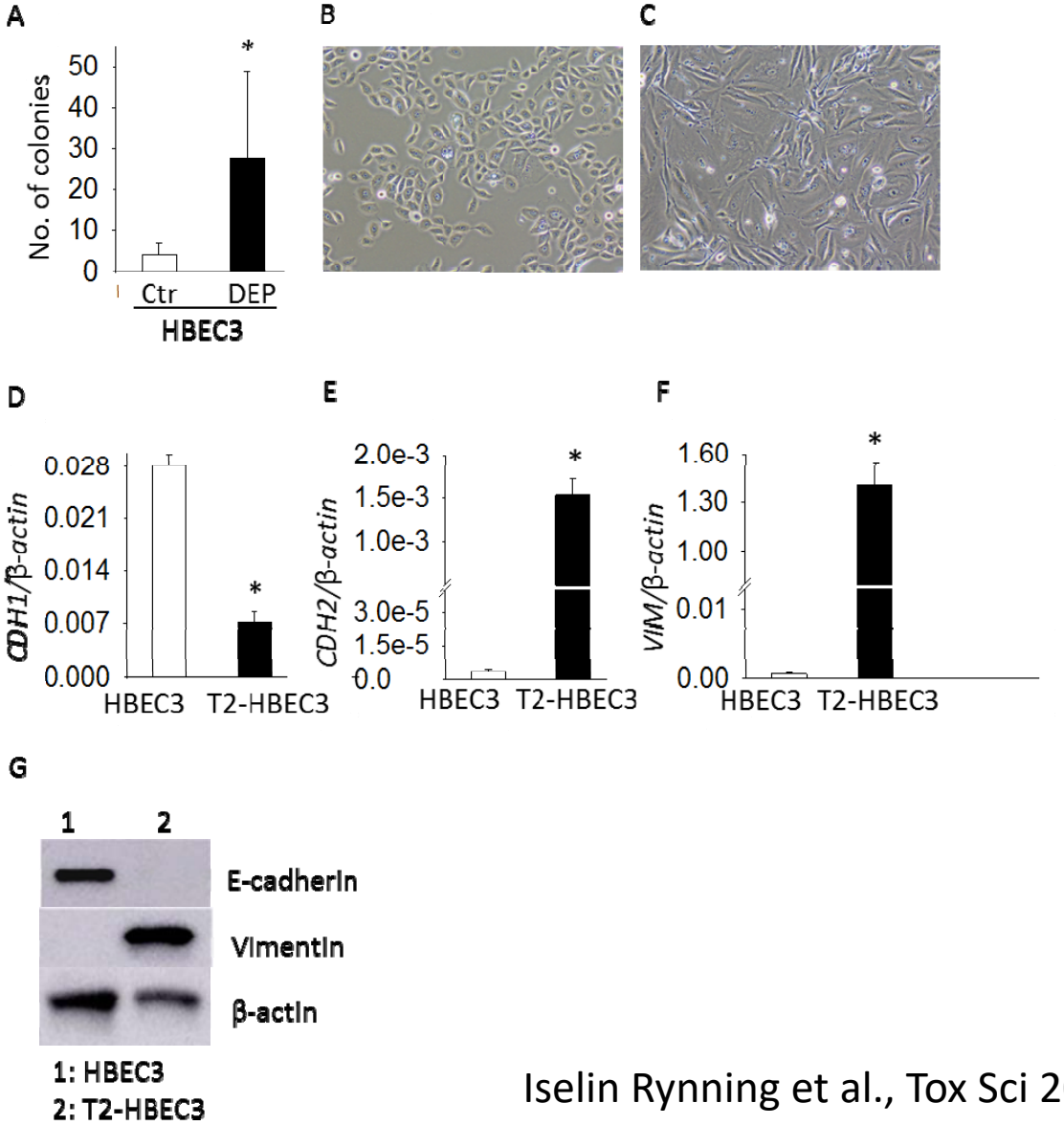
PM is linked to chronic inflammation: a milieu for cancer development



Adapted from Davies and Holgate 2002

Exposure of human bronchial epithelial cells (HBEC3) to DEP led to “cellular transformation”

DEP (NIST SRM2975) - transformed cells (T2-HBEC3): mesenchymal/fibroblast-like morphology, reduced CDH1 and enhanced CDH2 and VIM



Iselin Rynning et al., Tox Sci 2018, submitted

Deregulated genes between HBEC3 and T2-HBEC3 baseline

Gene expression profiling:
429 genes (224(↑) and (205↓)) were found to be significantly deregulated between HBEC3 and T2-HBEC3.

Genes were identified as being involved in regulation of cell migration and lung carcinogenesis:
DNER(↑), FBLN1(↑), HBEGF(↓), IGFBP3(↑), LAMA4(↑), PROS1(↑), RAB25(↓), SPOCK1(↑), ST14(↓), TGFBR3(↑), TP53INP1(↑), CD9(↓), CLDN1(↓), DUSP6(↓), EPCAM(↓), EPHA1(↓), FOXA2(↓), HAS3(↓), HTRA1(↑), MUC1(↑), PMEPA1(↑), TIMP2(↑), (EGR1(↓), EPHA1(↓), IL1B(↓), and VIM(↑).

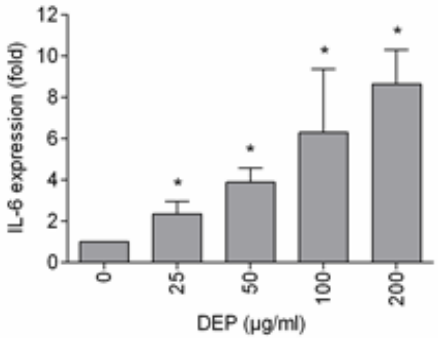
Deregulated genes between HBEC3 and T2-HBEC3 after short term DEP exposure

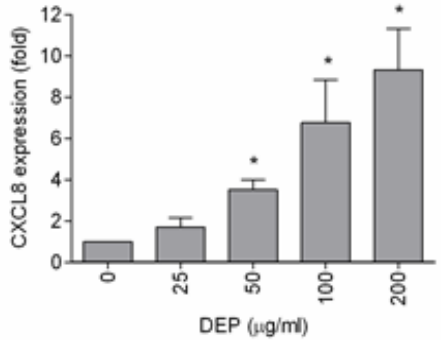
Four pathways were commonly deregulated in both HBEC3 and T2-HBEC3 in the short-term DEP-exposure experiments: "Tryptophan metabolism", "Valine, leucine and isoleucine degradation", "Terpenoid backbone biosynthesis" and "Steroid biosynthesis". Three pathways were significantly deregulated in HBEC3, only: "Metabolism of xenobiotics by cytochrome p450", "Phagosome" and "Aldosterone-regulated sodium reabsorption". In T2-HBEC3, several pathways associated with inflammatory responses were identified in addition to "Synthesis and degradation of ketone bodies", "Butanoate metabolism" and "Pyruvate metabolism".

Differences between HBEC3 and T2-HBEC3 regarding *steady-state levels* and *DEP-induced changes* of particularly ***CYP1A1, IL-1β, PGE2 and PGF2α*** may have implications for acute inflammation and carcinogenesis.

Iselin Rynning et al., Tox Sci 2018, submitted

Inflammatory responses of DEP (MAPCEL soot) in BEAS-2B

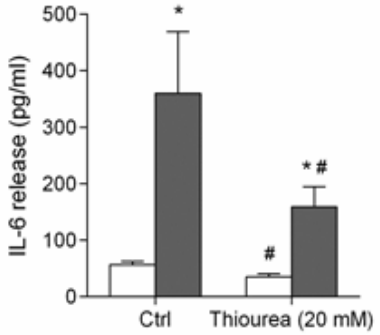


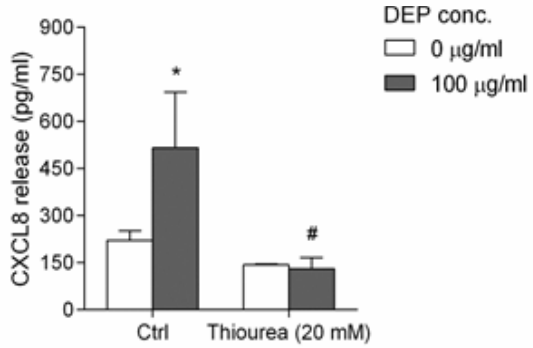


Increased expression and release:

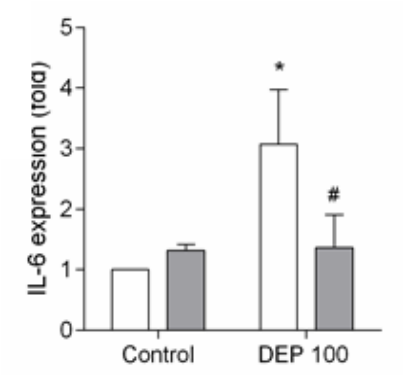
IL-6: pro-inflammatory cytokine

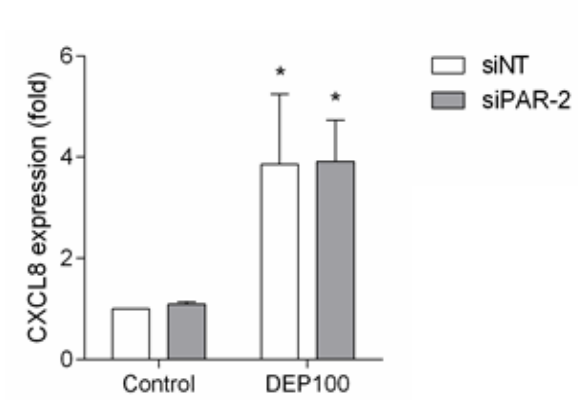
IL-8/CXCL8: chemokine





Role of ROS/ REM





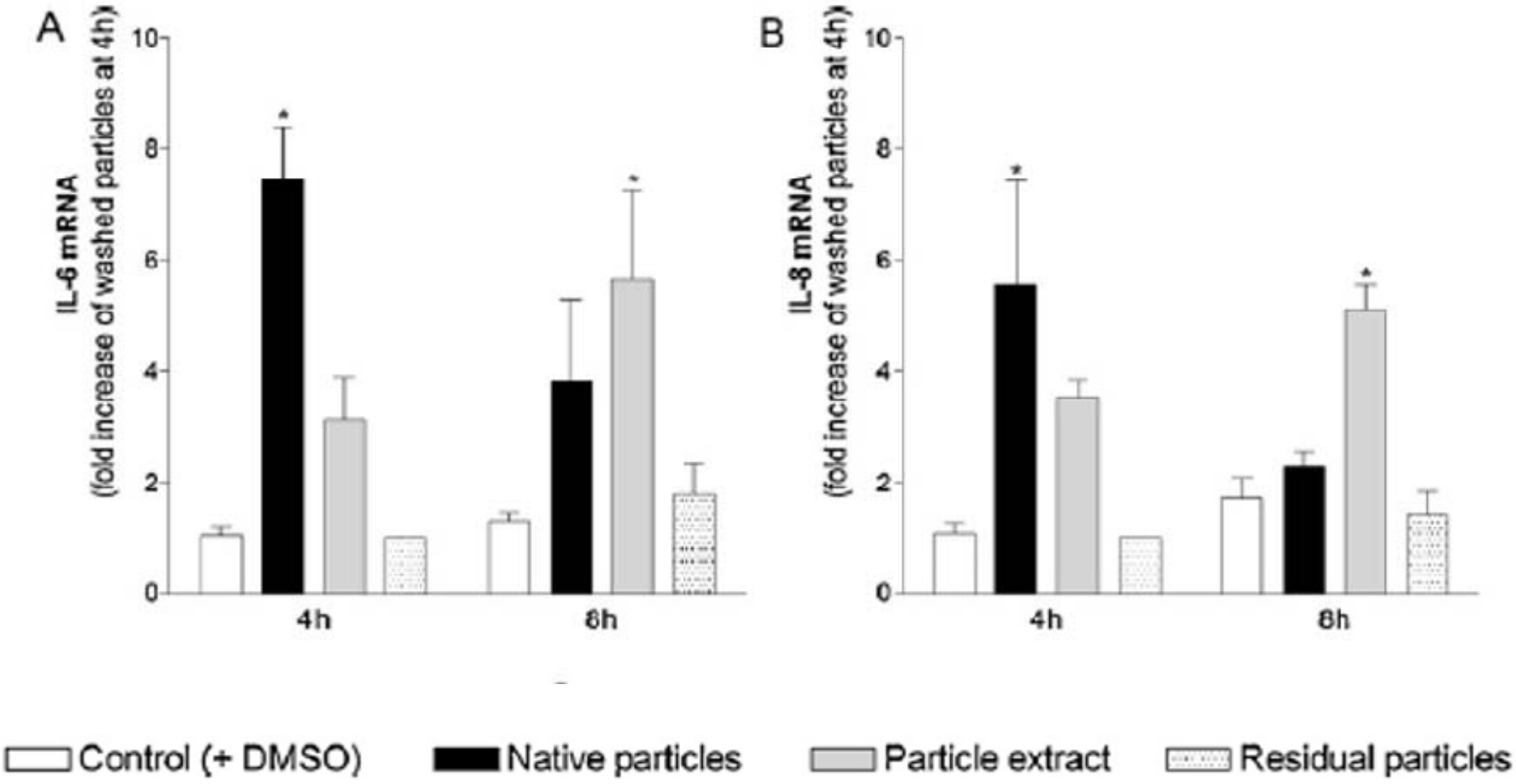
DEP via PAR-2, regulate matrix metalloproteinase-1 (MMP-1) and calcium influx through TRPV4-channels (Lie et al, Environ. Health Perspect 2011)

Role of PAR-2
(protein activated receptor-2)

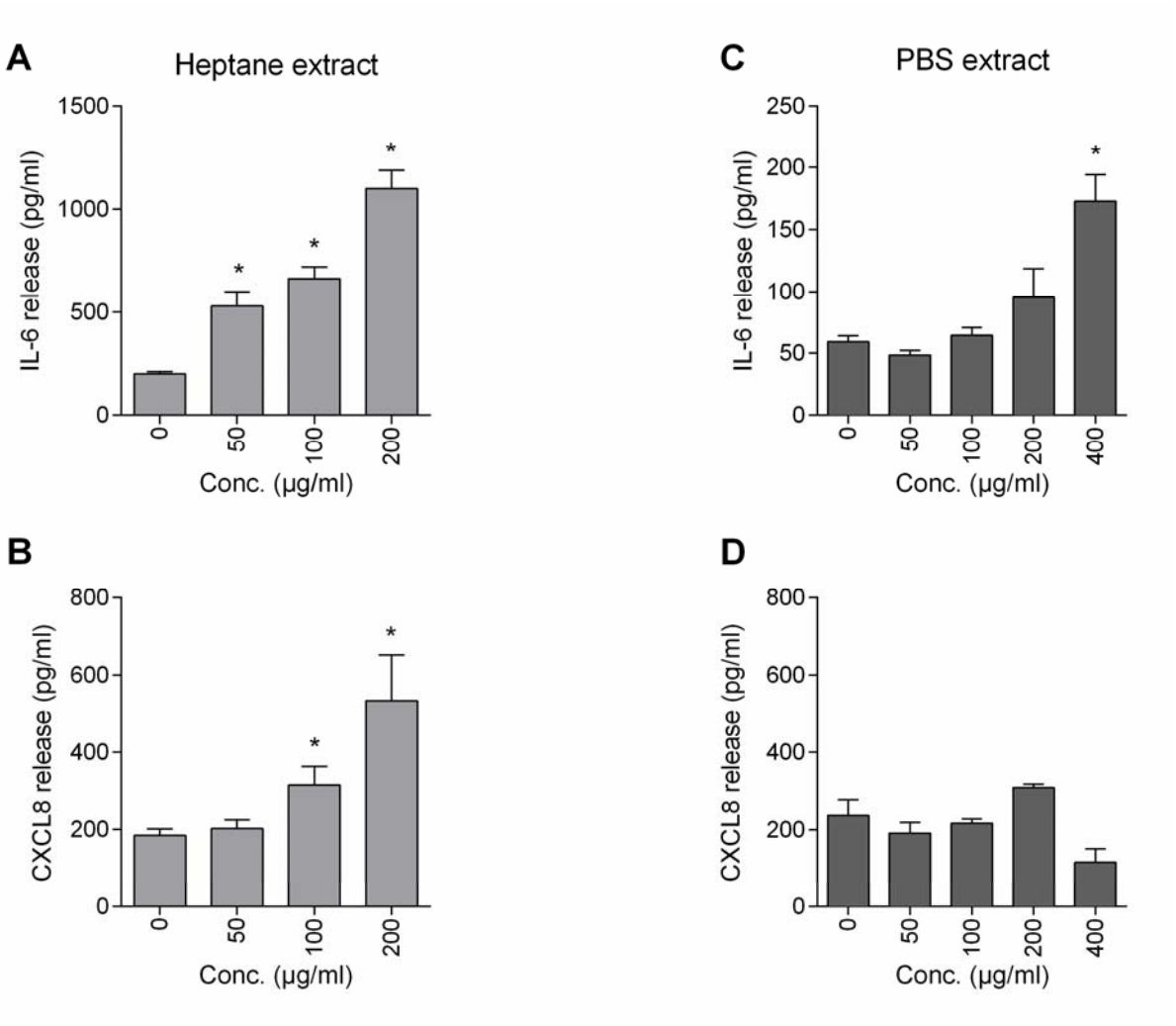
N Bach et al, Tox Lett 2015

Proinflammatory responses:
mainly due to extractable organic compounds

AI. Totlandsdal et al. / Toxicology Letters 208 (2012) 262–268



Inflammatory responses of extracts of DEP in BEAS-2B cells

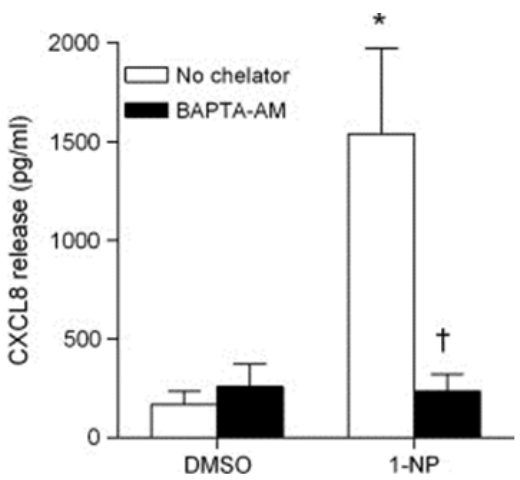


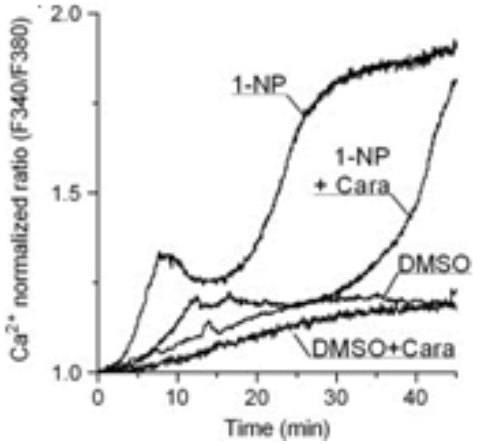
Non-polar

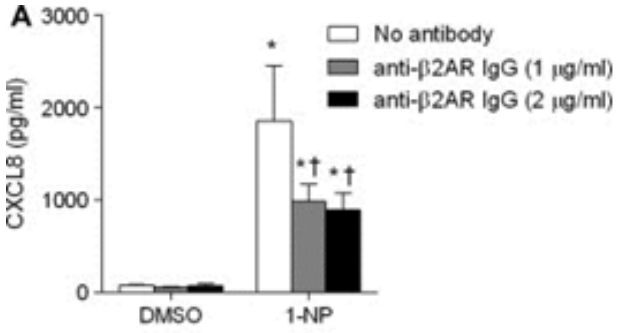
Highly polar

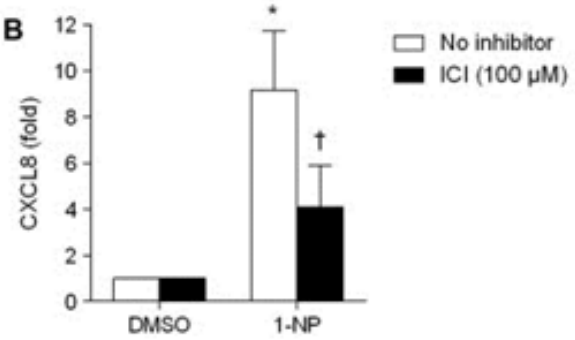
N Bach et al, Tox Lett 2015

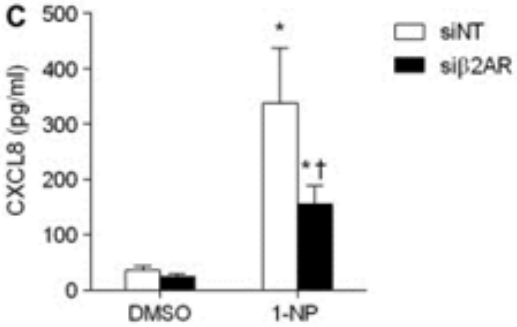
1-NP-induced IL-8/ CXCL8: β2-adrenergic receptor (AR) linked Ca^{2+} release





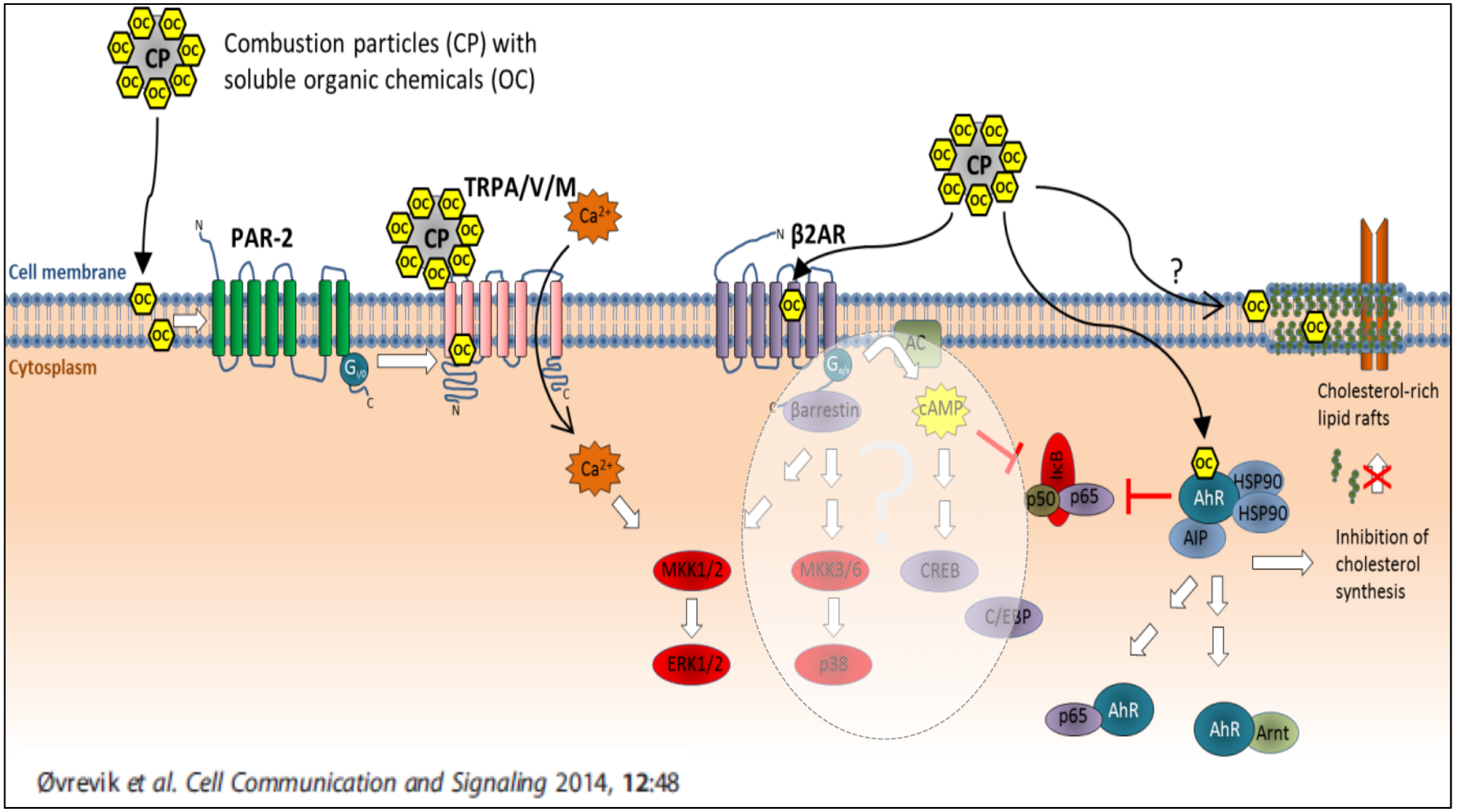






A Mayati / J Øvrevik et al, Toxicol In Vitro, 2014

Inflammatory trigging points



Collaborators:

Norwegian Inst. of Public Health (NO)

Johan Ovrevik
Marit Låg
Magne Refsnes
Anette K. Bølling
Annike I. Totlandsdal
Anita Solhaug
Per E. Schwarze
Nicolai Bach
Bendik Brinchmann
Tonje Skuland
Edel Lilleaas
Hans Jørgen Dahlmann
Leni Ekren

National Institute of Occupational Health (NO)

Steen Mollerup
Anani K. J. Afanou,
Øivind Skare,
Iselin Rynning,
Yke J. Arnoldussen,
Aage Haugen,

University of Rennes/Inserm U620 (Fr)

D Lagadic-Gossmann, E le Ferrec, A Mayati, V Lecureur

Vet Res Inst and Inst Exp Med (CR)

J Neca, E Hruba, M Machala, P Rossner, Jr., K Vrbova, H Libalova, J Topinka

University of North Dakota (USA)

A Kubátová, R E Cochran, K Ondrušová

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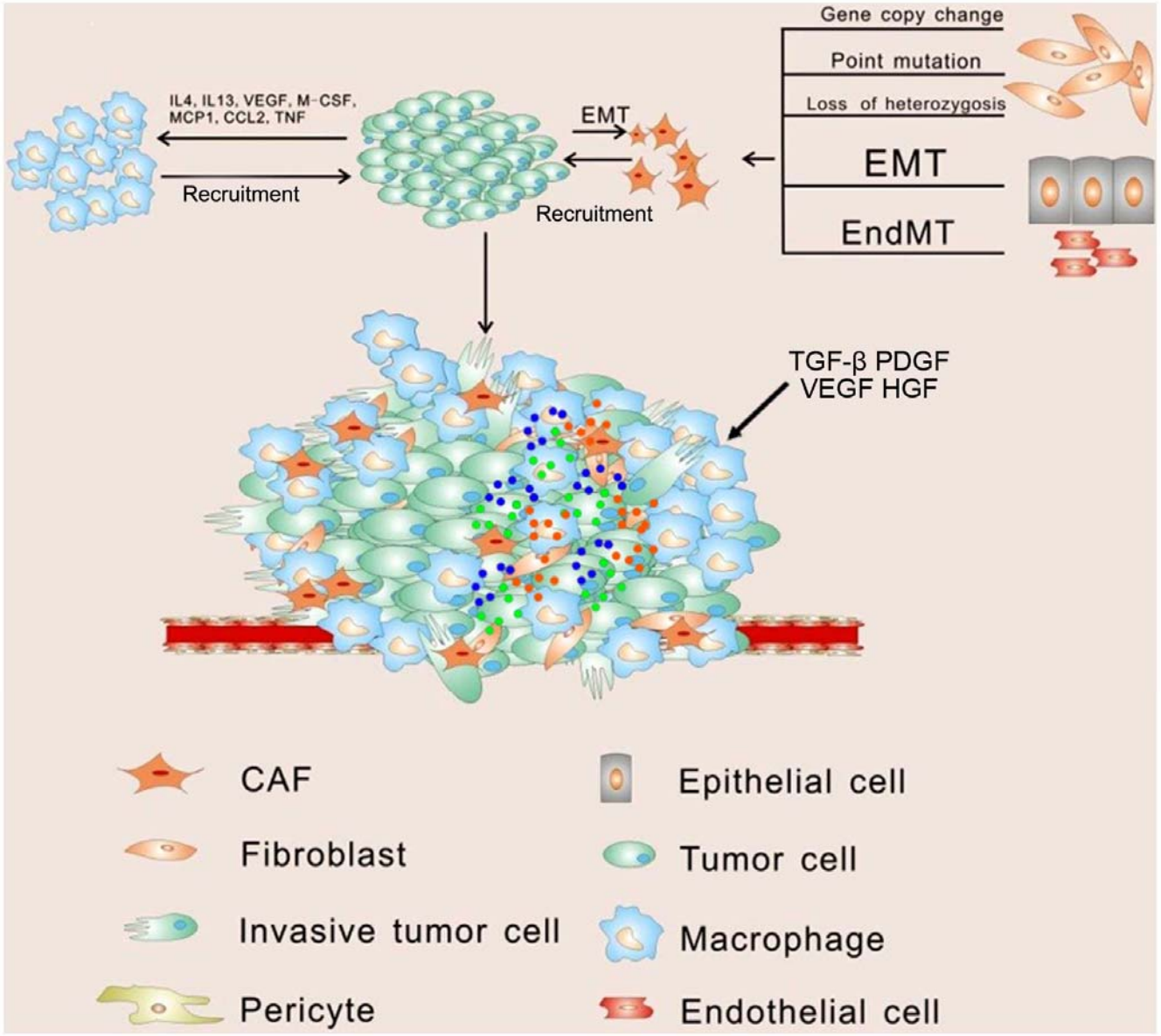
Lung Cancer Development

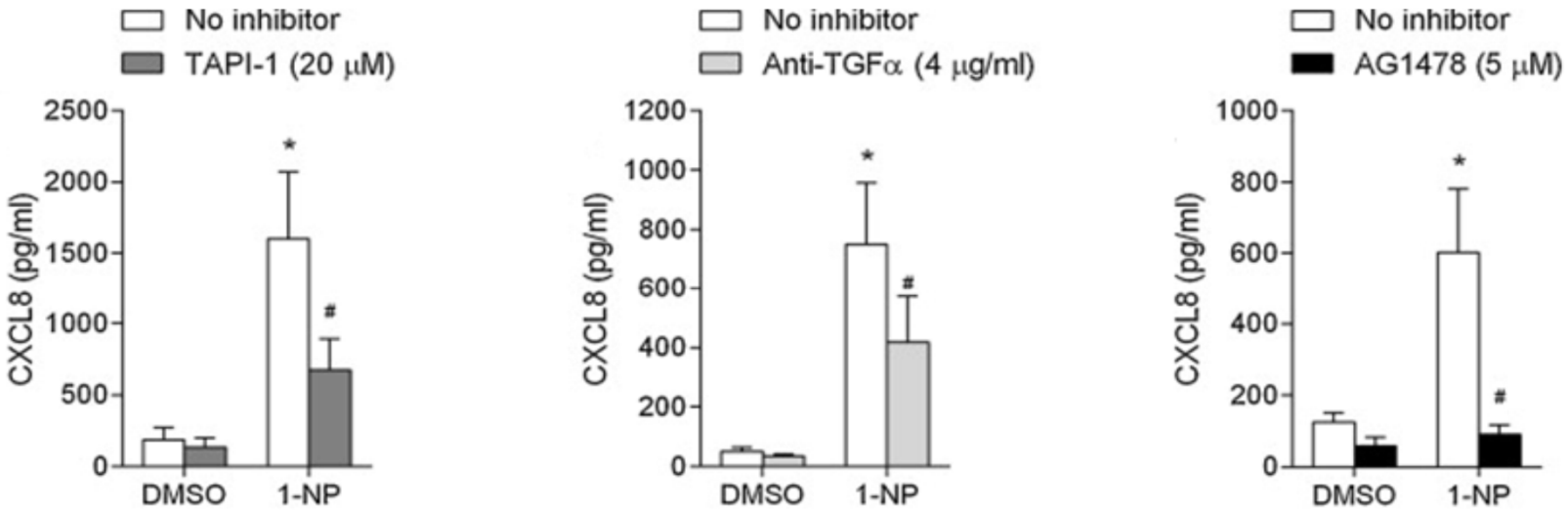
initiation, formation and progression,
matrix remodeling, intravasation, extravasation and metastasis

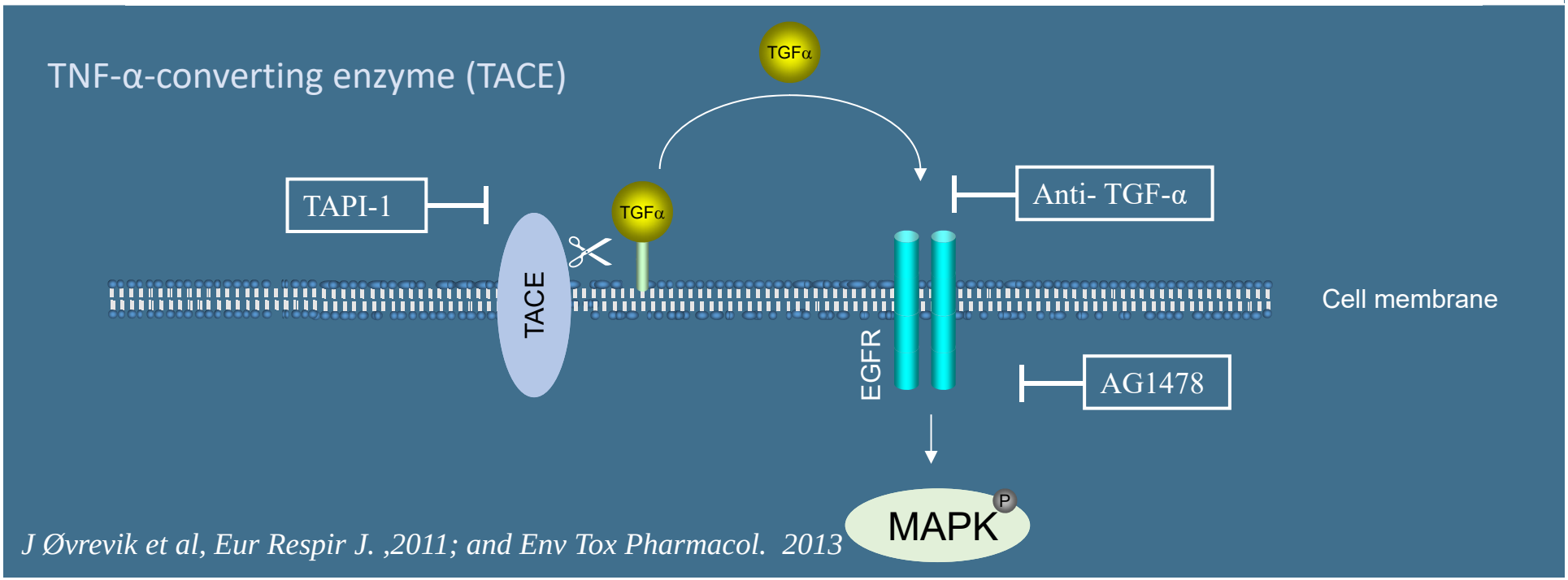


EMT: epithelial-to-mesenchymal-transition

Yao Yuan, et al
Oncology Reports 2016

1-NP-induced IL-8/ CXCL8: Role of TACE/ TGFα/ EGFR





J Øvrevik et al, Eur Respir J. ,2011; and Env Tox Pharmacol. 2013