Macrophages, inflammation and lung cancer in 2021

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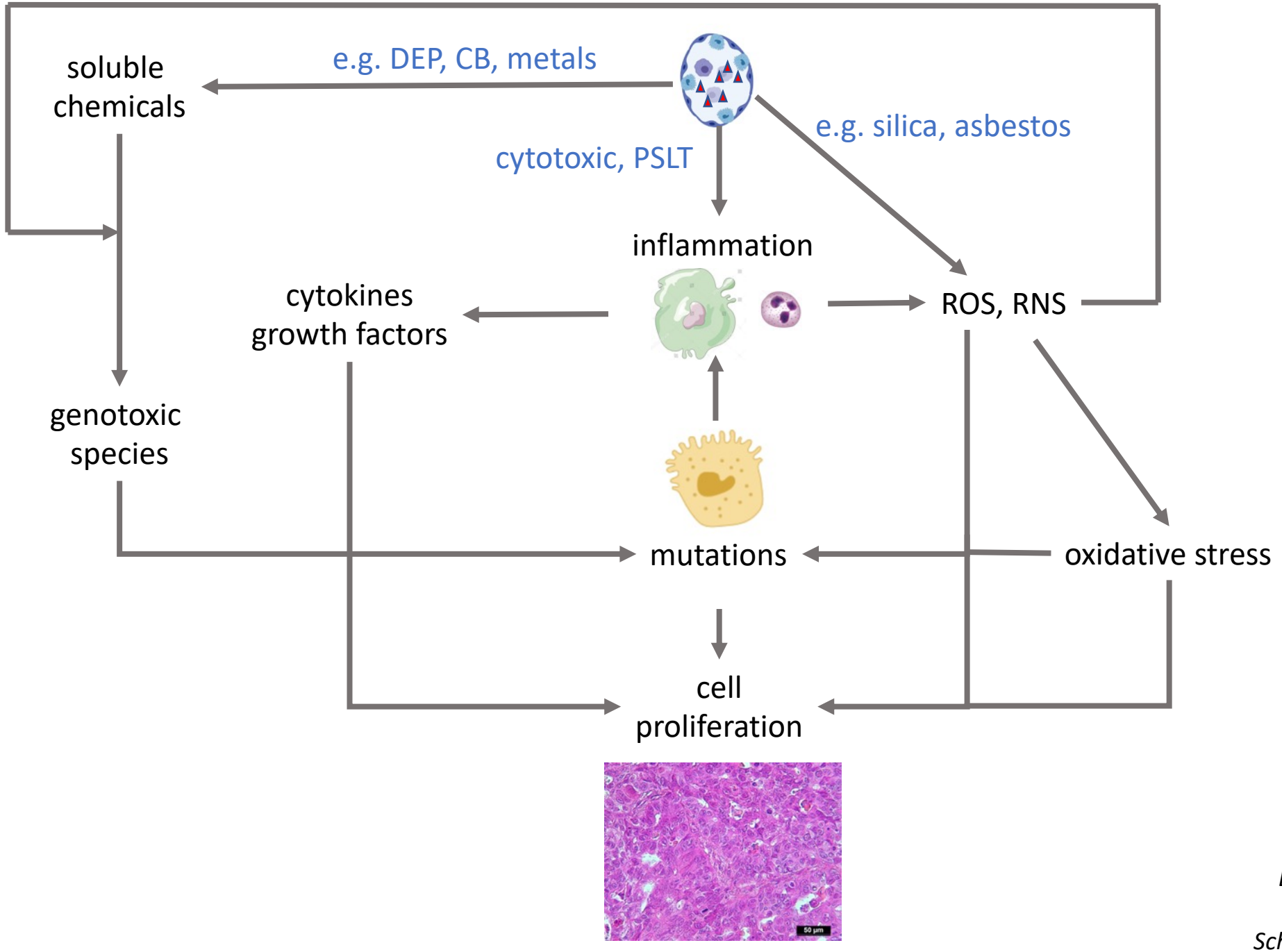
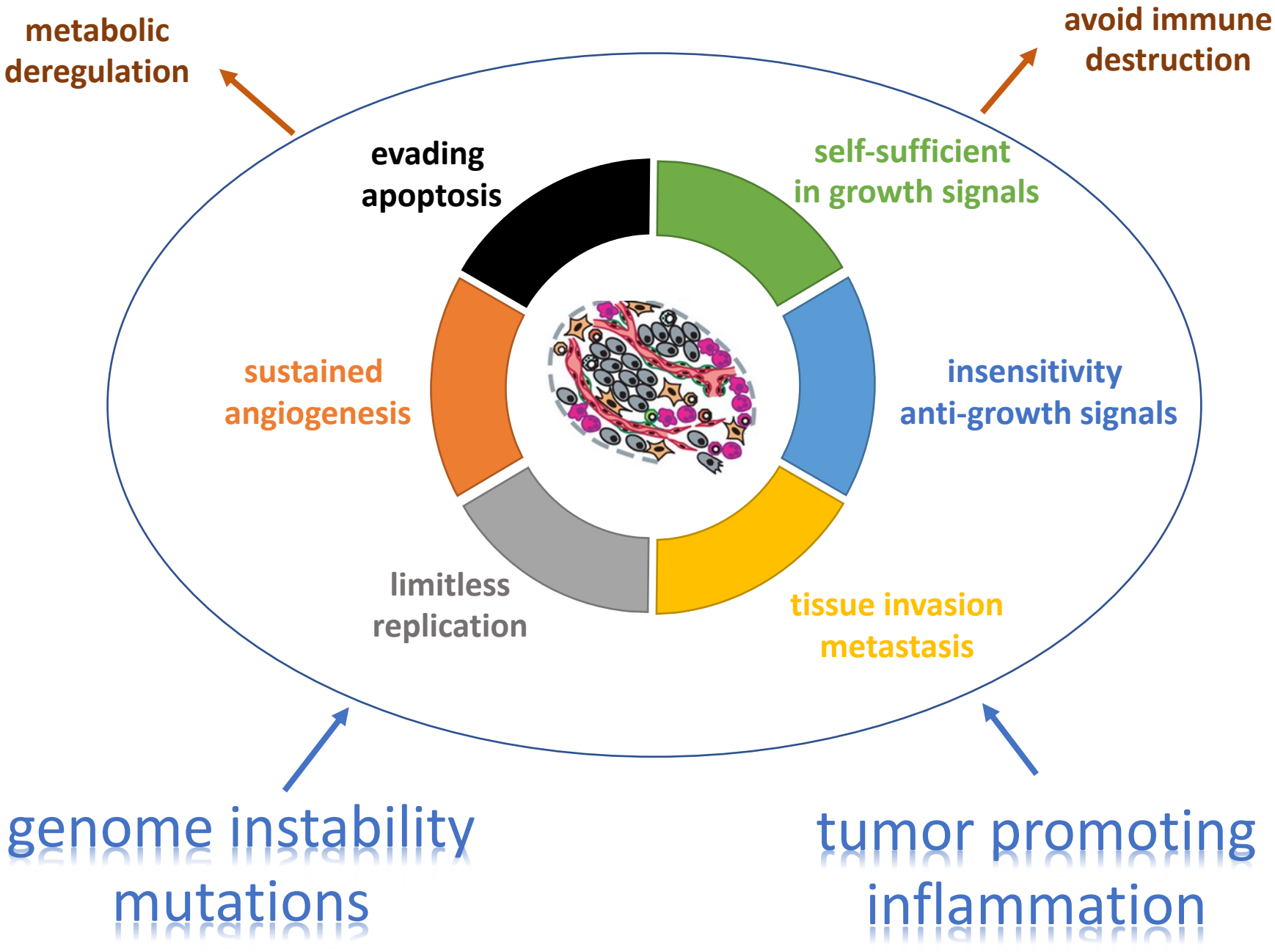
Current paradigm in particle toxicology?



Borm & Driscoll, 1996
Knaapen et al., 2004
Schins & Knaapen, 2007

What have we learned in recent years?



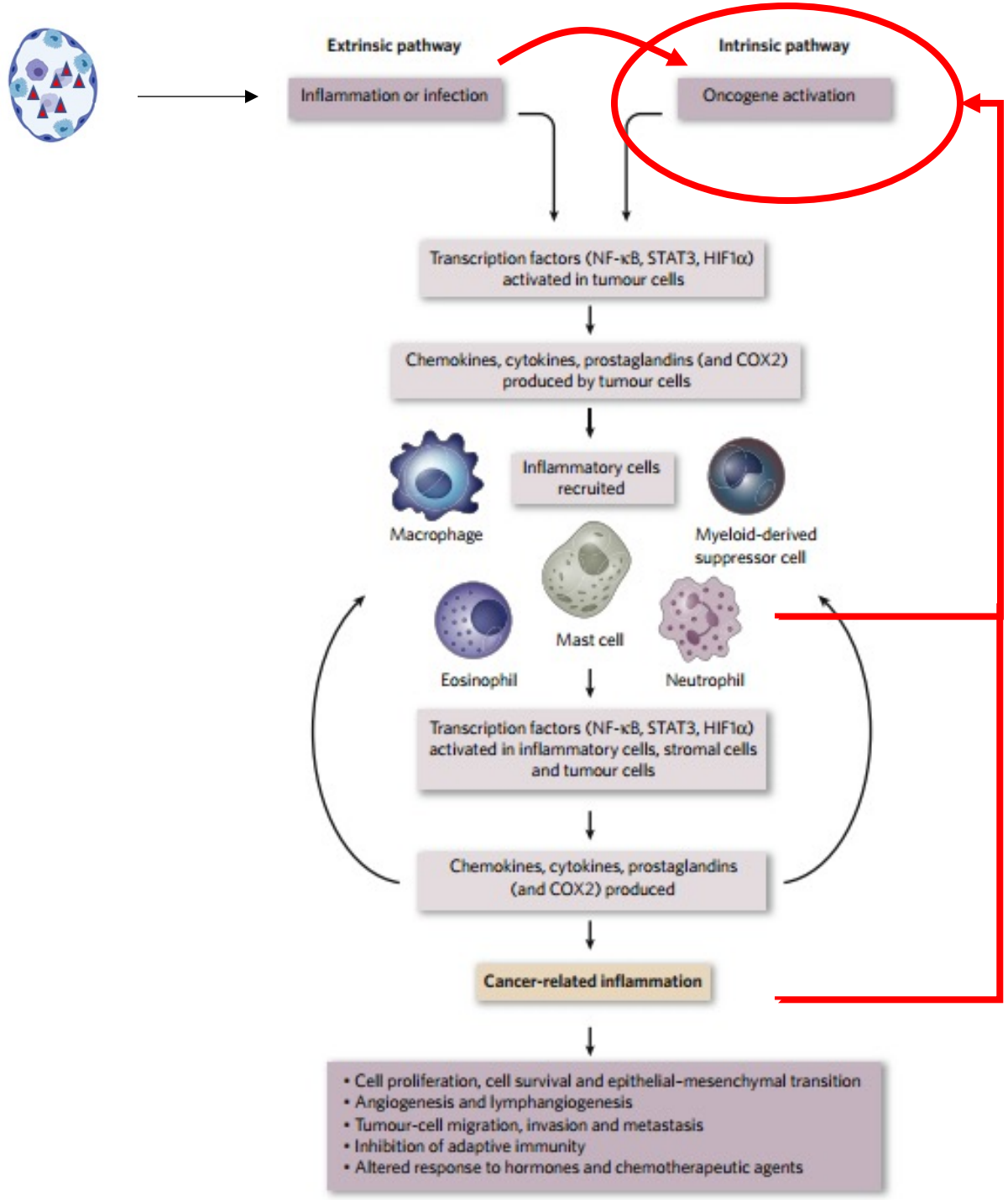
Hanahan & Weinberg, 2011
Senga & Grose, 2021

Inflammation promotes cancer development

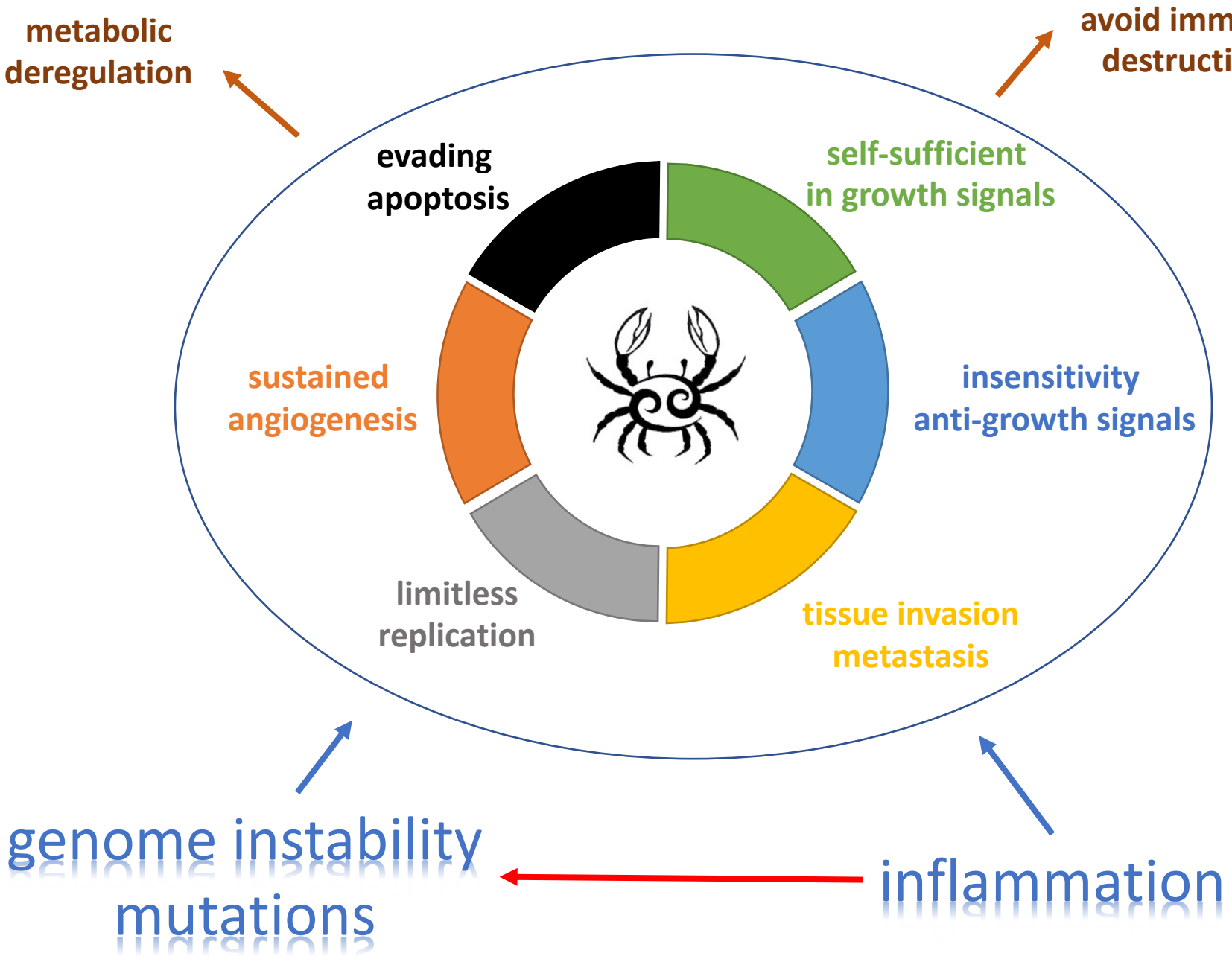
Early :

- inducing genomic instability (secondary genotoxicity)
- facilitating genomic instability (cell proliferation)
- promoting angiogenesis
- regulating the growth, migration and differentiation of neoplastic cells, fibroblasts and endothelial cells

= attractive environment for tumour growth



Mantovani et al., 2008



Hanahan & Weinberg, 2011
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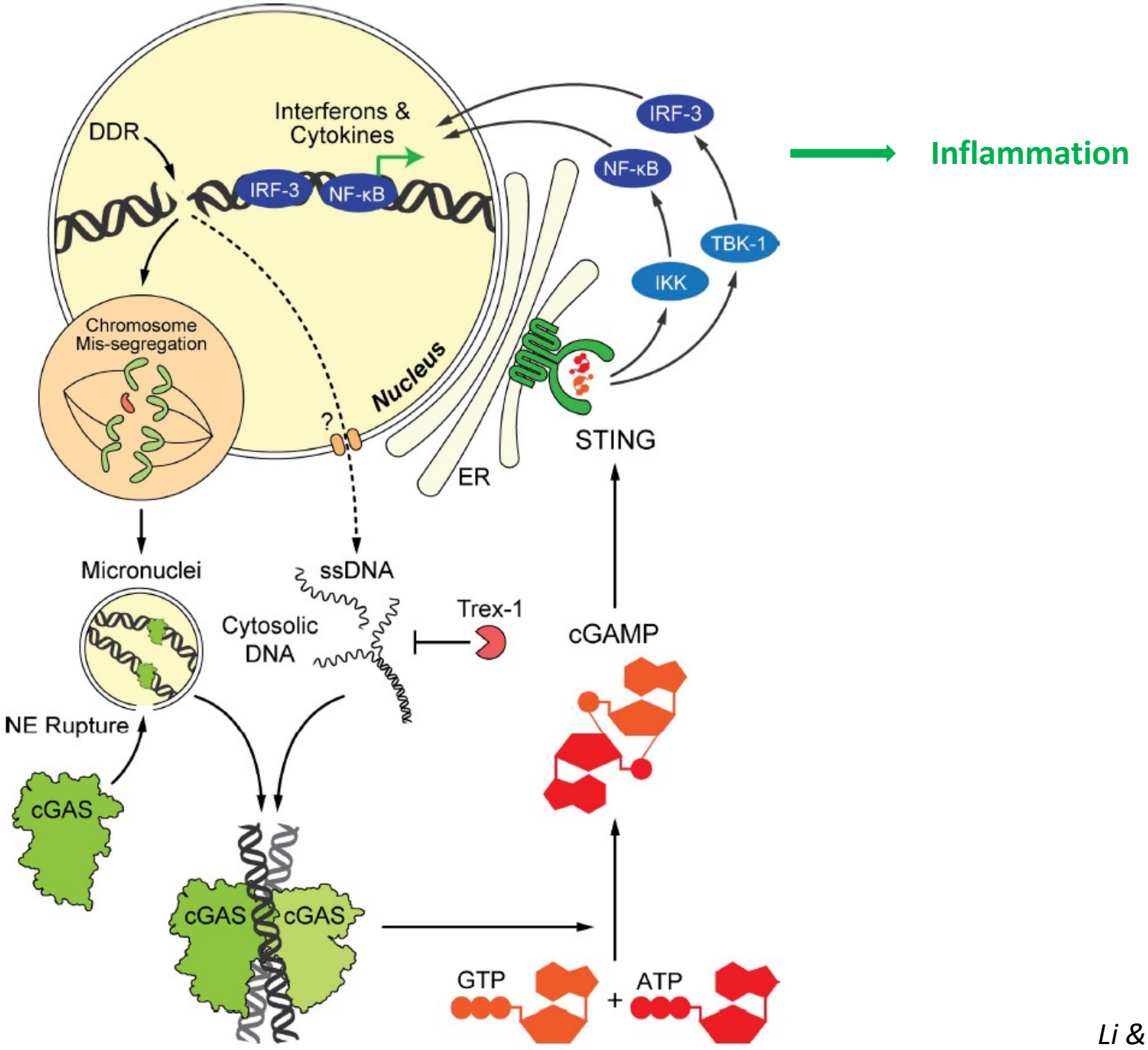
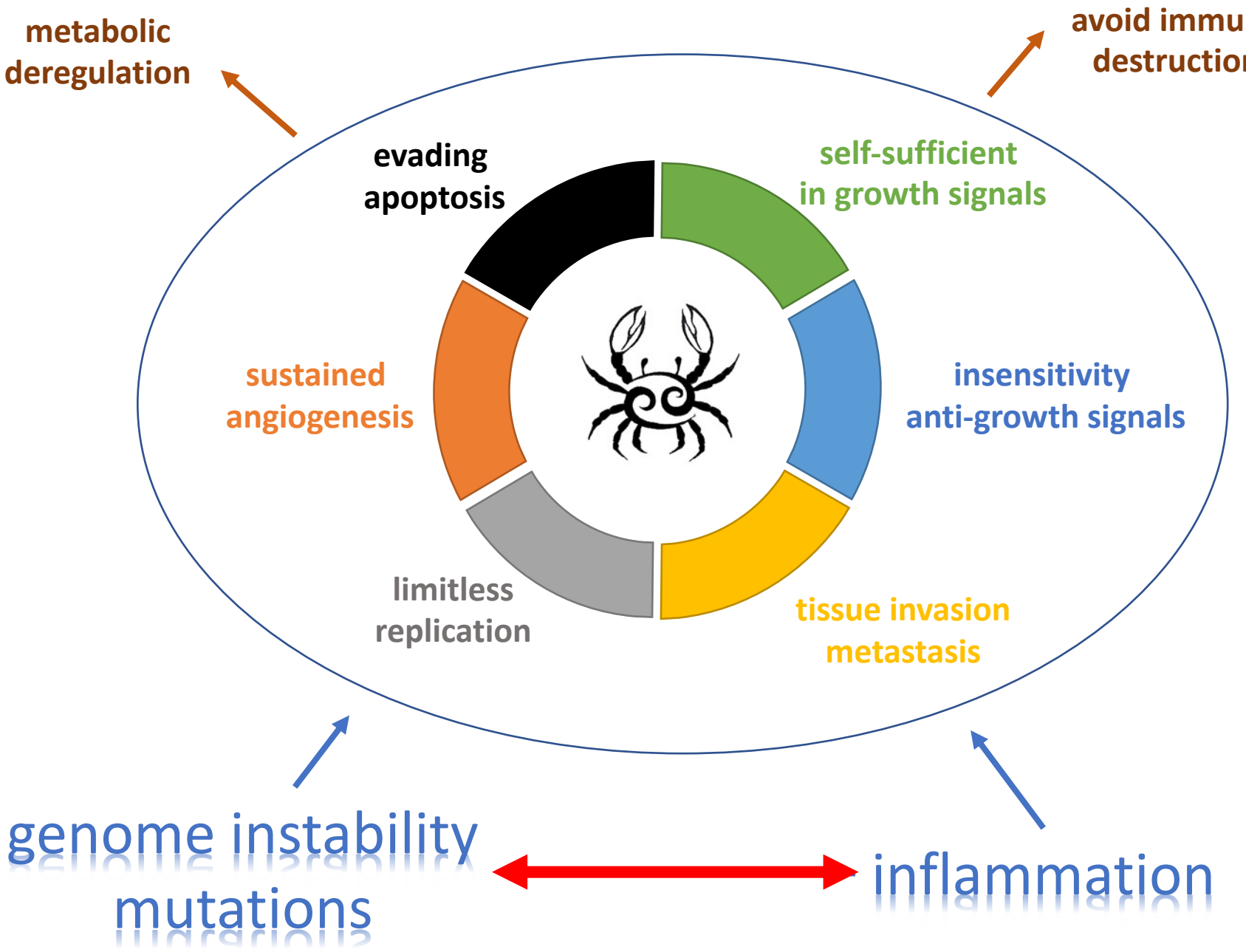
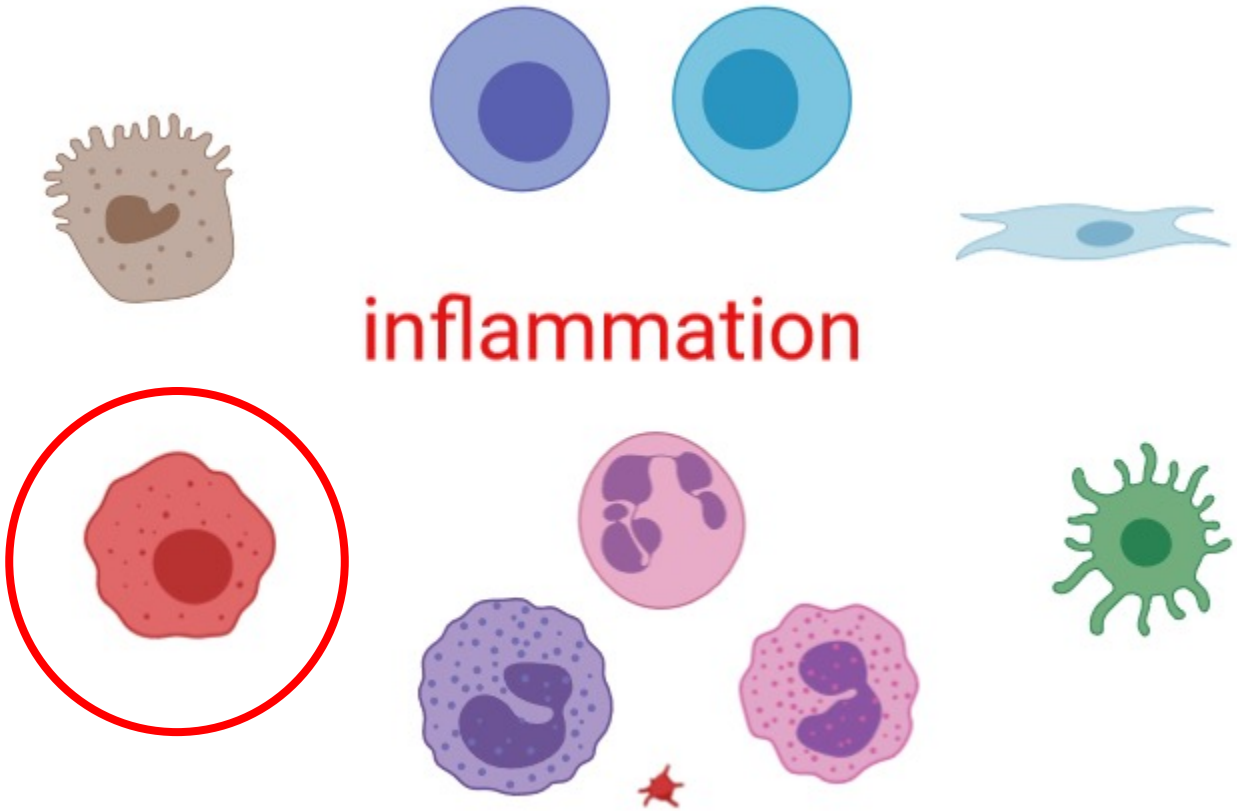
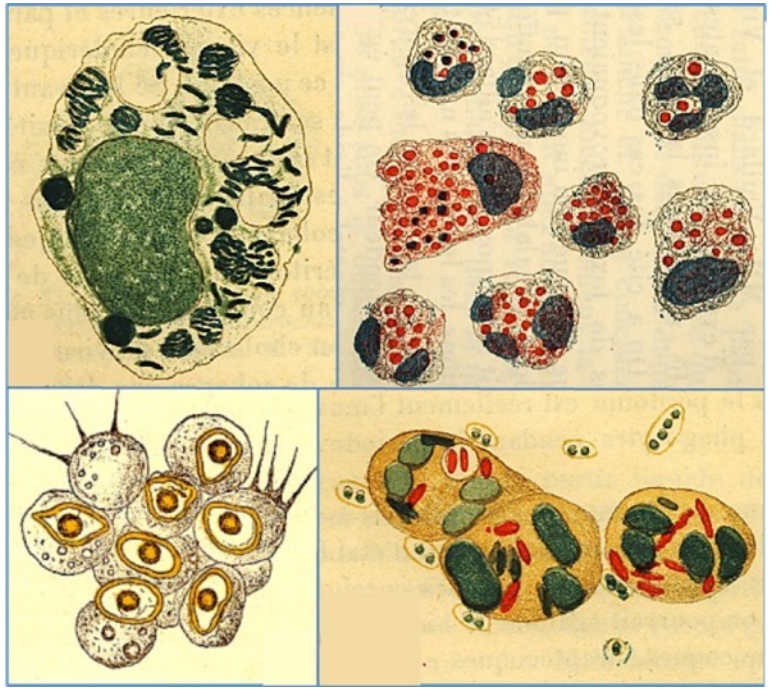

DDR
Interferons &
Cytokines
IRF-3
NF-κB
IRF-3
NF-κB
TBK-1
IKK
Chromosome
Mis-segregation
Nucleus
?
ER
STING
Micronuclei
ssDNA
Cytosolic
DNA
Trex-1
cGAMP
NE Rupture
cGAS
cGAS
cGAS
GTP
+
ATP
Inflammation

Li & Chen, 2018



Hanahan & Weinberg, 2011
Senga & Grose, 2021


inflammation



“the essence of an inflammation lies in the phagocyte attack of solid pathogenic substances, be it a weakened or dead cell, a bacterium or any other foreign body”

Metchnikov 1891

Macrophages in 2021 ?

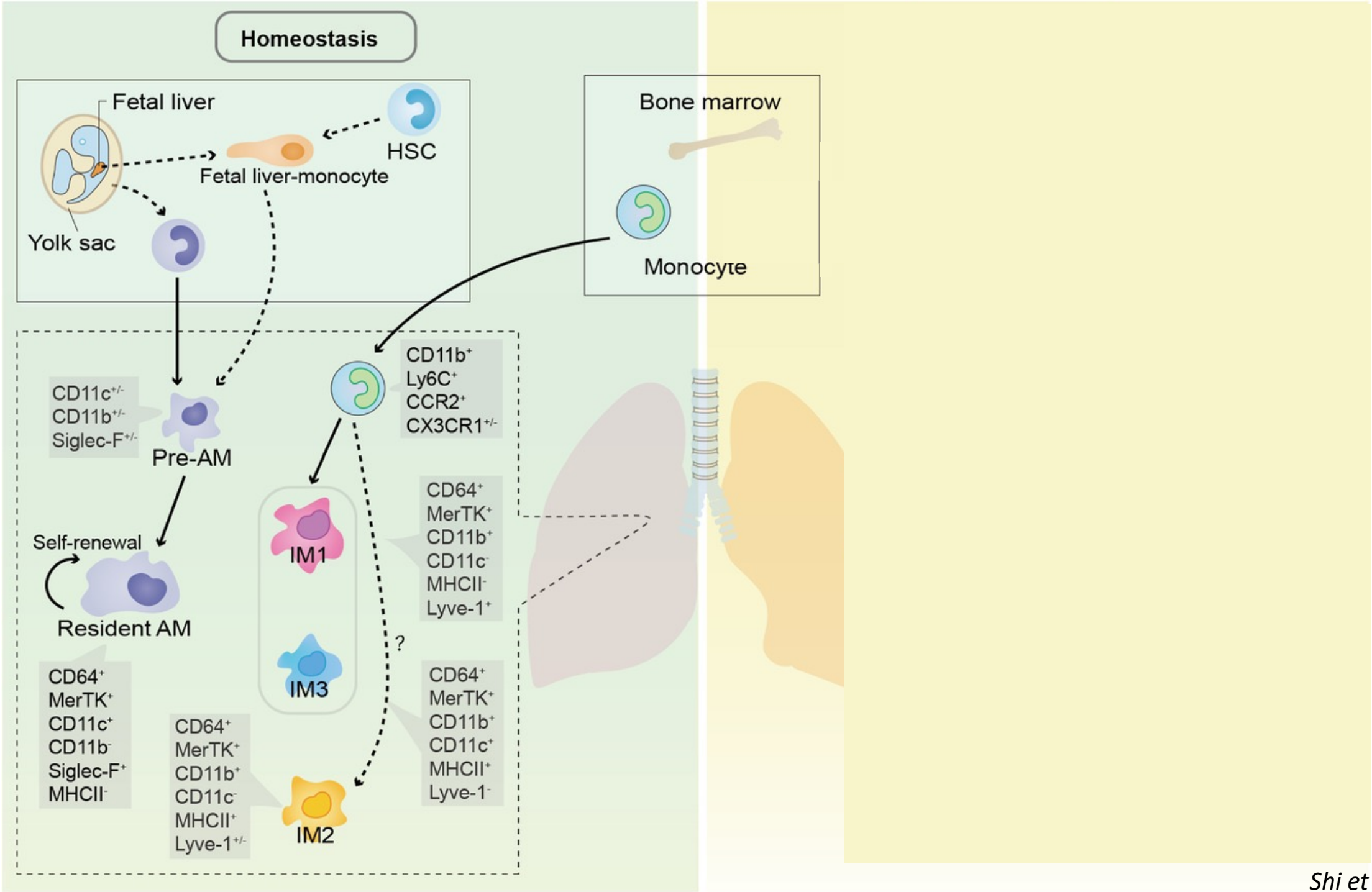
Mouse
Humans
Rat

- lung macrophage DIVERSITY
  - ontogeny
  - phenotypic heterogeneity
    environment
    microtopology
  - functional heterogeneity

- tumor-associated macrophages (TAM)

macrophage diversity

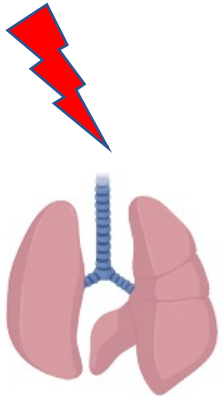
influence of ontogeny



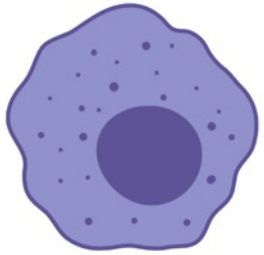
Shi et al., 2020

The alveolar macrophages

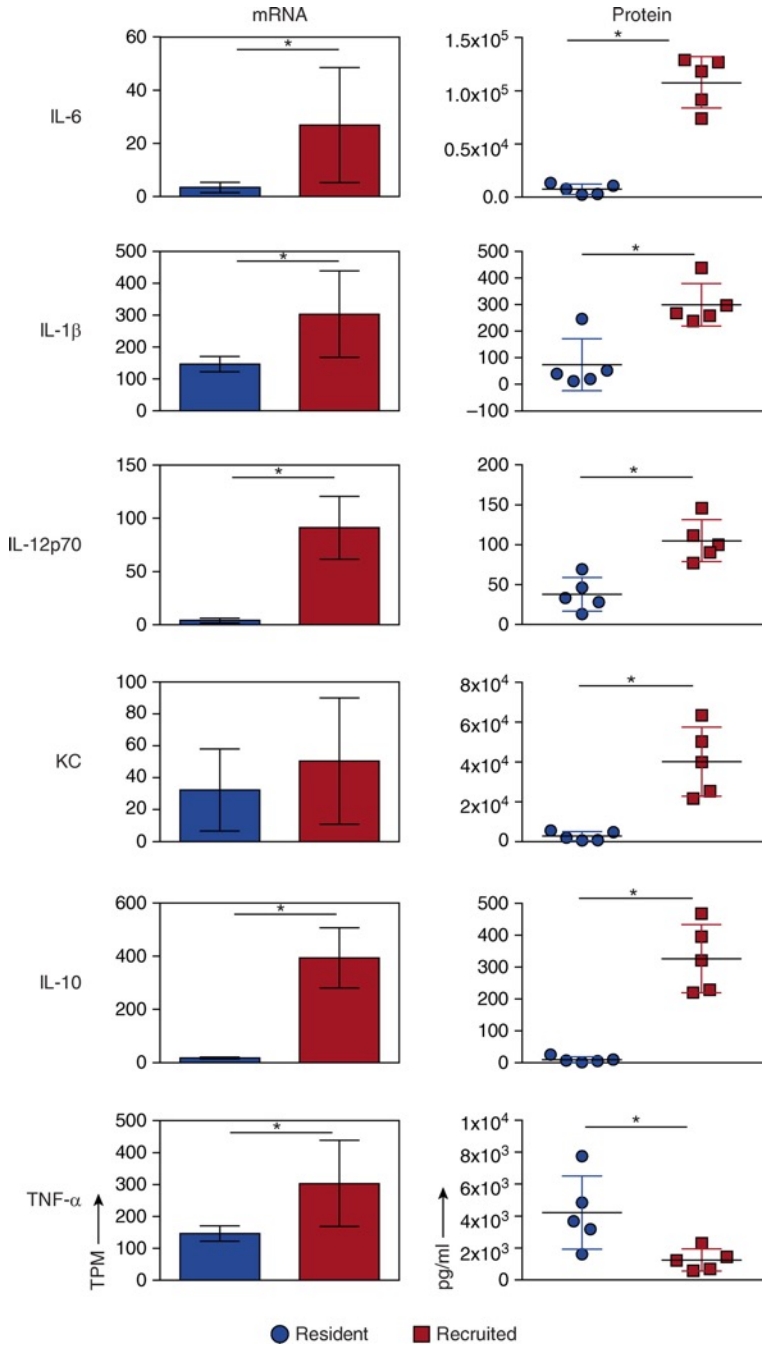
LPS



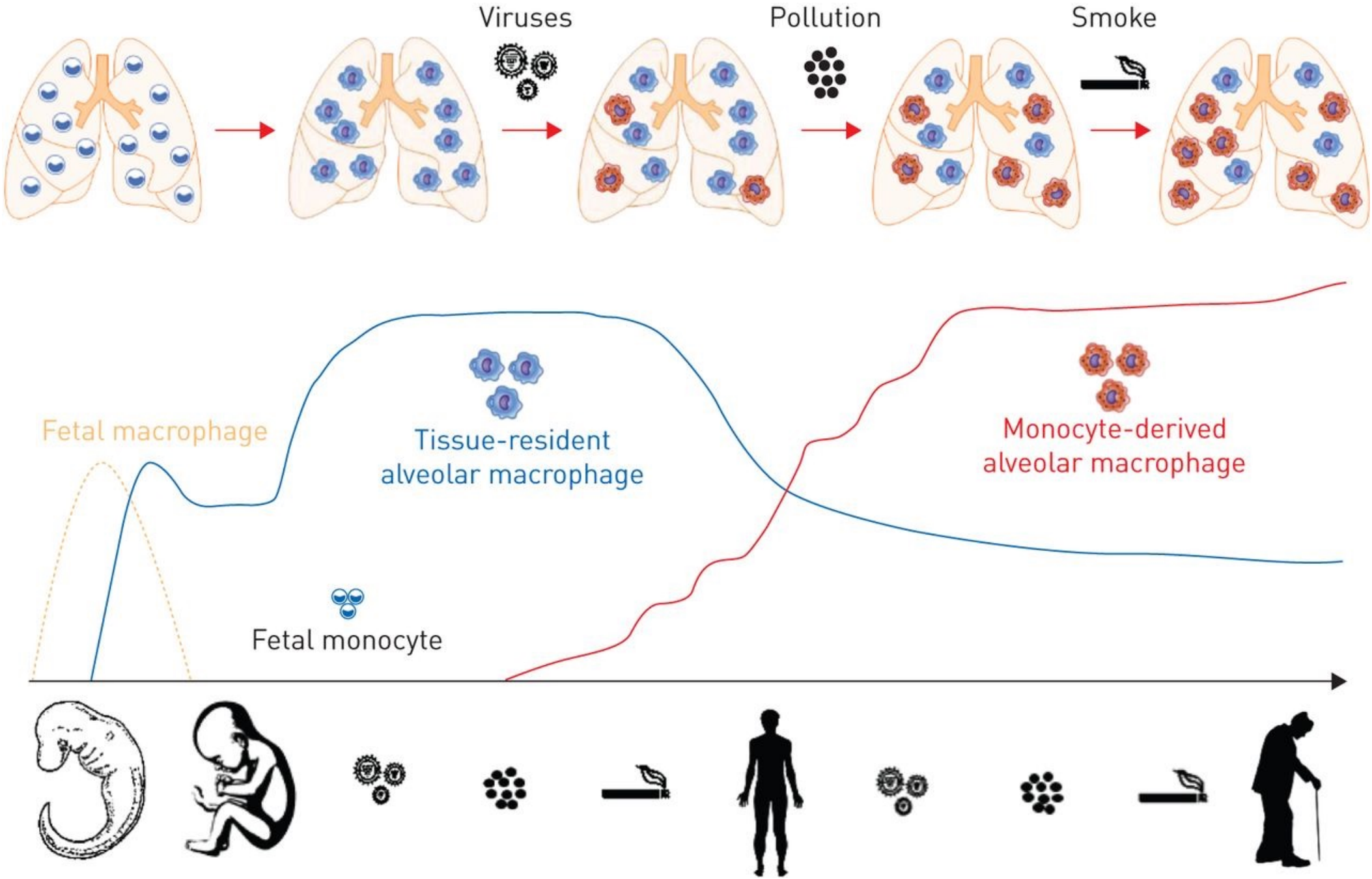
embryonic
(resident)
CD11c^{high}, CD11b^{low}



monocyte-derived
(recruited)
CD11c^{low}, CD11b^{high}



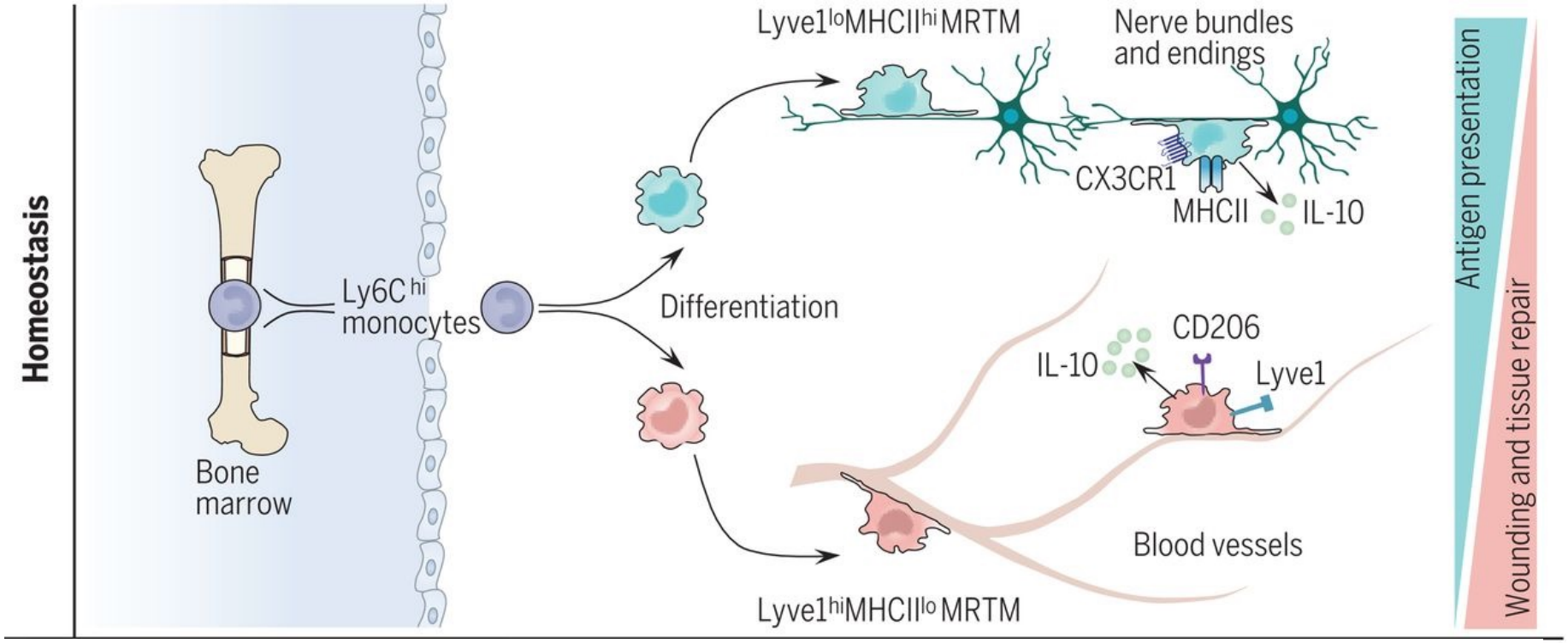
Mould et al., 2017



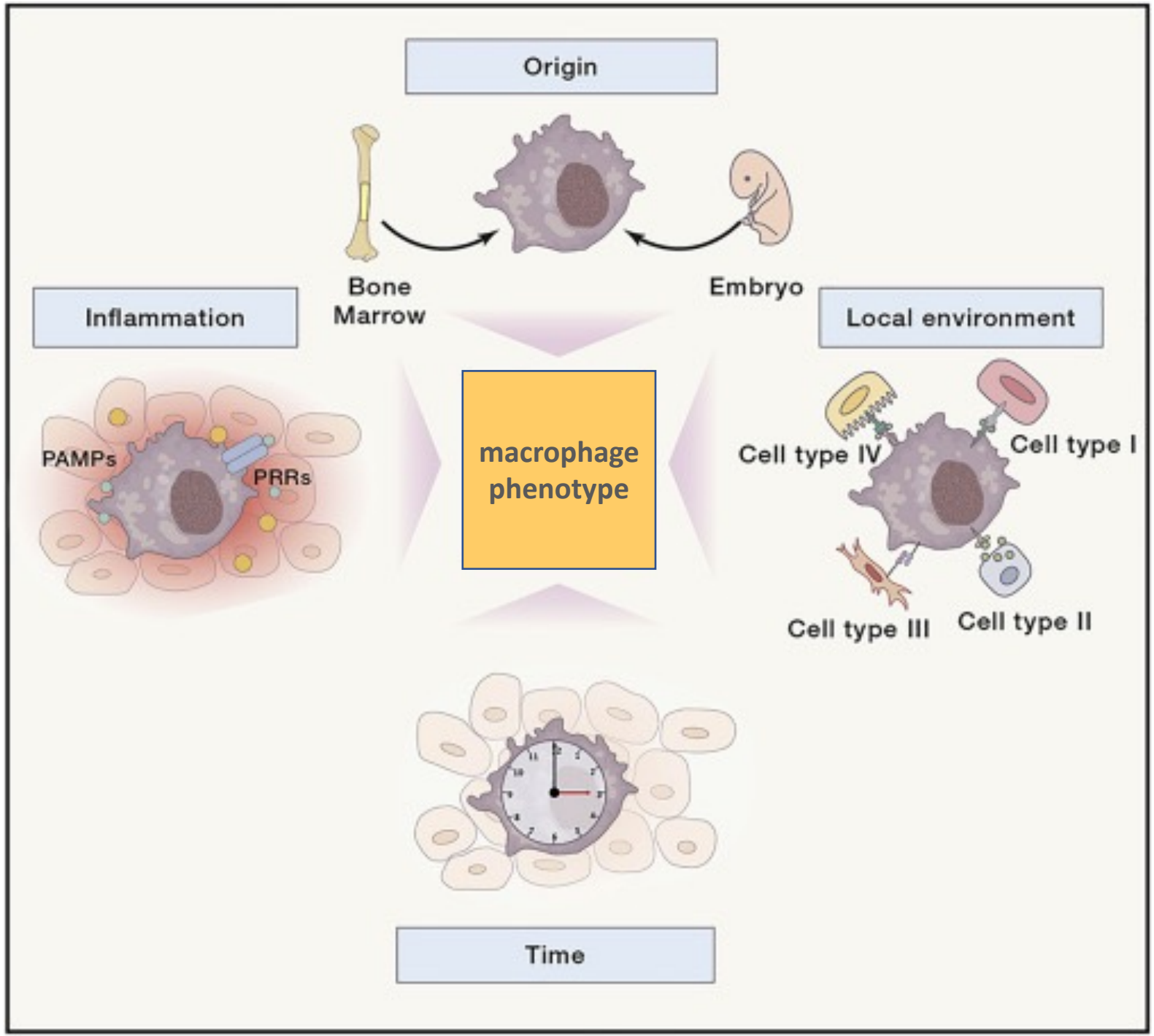
Morales-Nebreda et al., 2015

macrophage diversity

influence of microenvironment



Nobs & Kopf, 2021
Chakarov et al, 2019



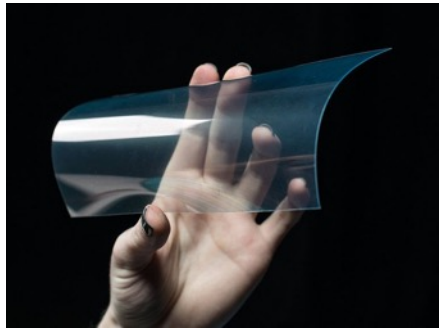
Blériot et al., 2020

In_2O_3 SnO

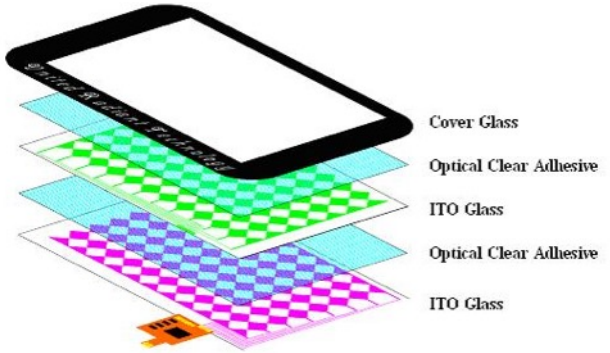
90% **10%**

sintering

sputtering



ITO



J Occup Health 2003; 45: 137–139

Rapid Communication

Interstitial Pneumonia Developed in a Worker Dealing with Particles Containing Indium-tin Oxide

Toshiaki HOMMA[1], Takahiro UENO[1], Kiyohisa SEKIZAWA[1], Akiyo TANAKA[2] and Miyuki HIRATA[2]

[1]Department of Respiratory Diseases, Institute of Clinical Medicine, University of Tsukuba, [2]Department of Hygiene, Graduate School of Medical Sciences, Kyushu University, Japan

Key words: Indium-tin oxide, Interstitial pneumonia, Indium

The use of indium compounds in the electronics and semiconductor industry has risen sharply from the 1990s, and indium demand increased to a record 335 tons in 2000 in Japan, which was about 5 times that in 1990[1)]. Indium-tin oxide (ITO) is a sintered alloy containing a large portion of indium oxide and a small portion of tin oxide, and is used in the making of thin-film transistor liquid crystal displays (LCDs) for television screens, portable computer screens, cell phone displays and video

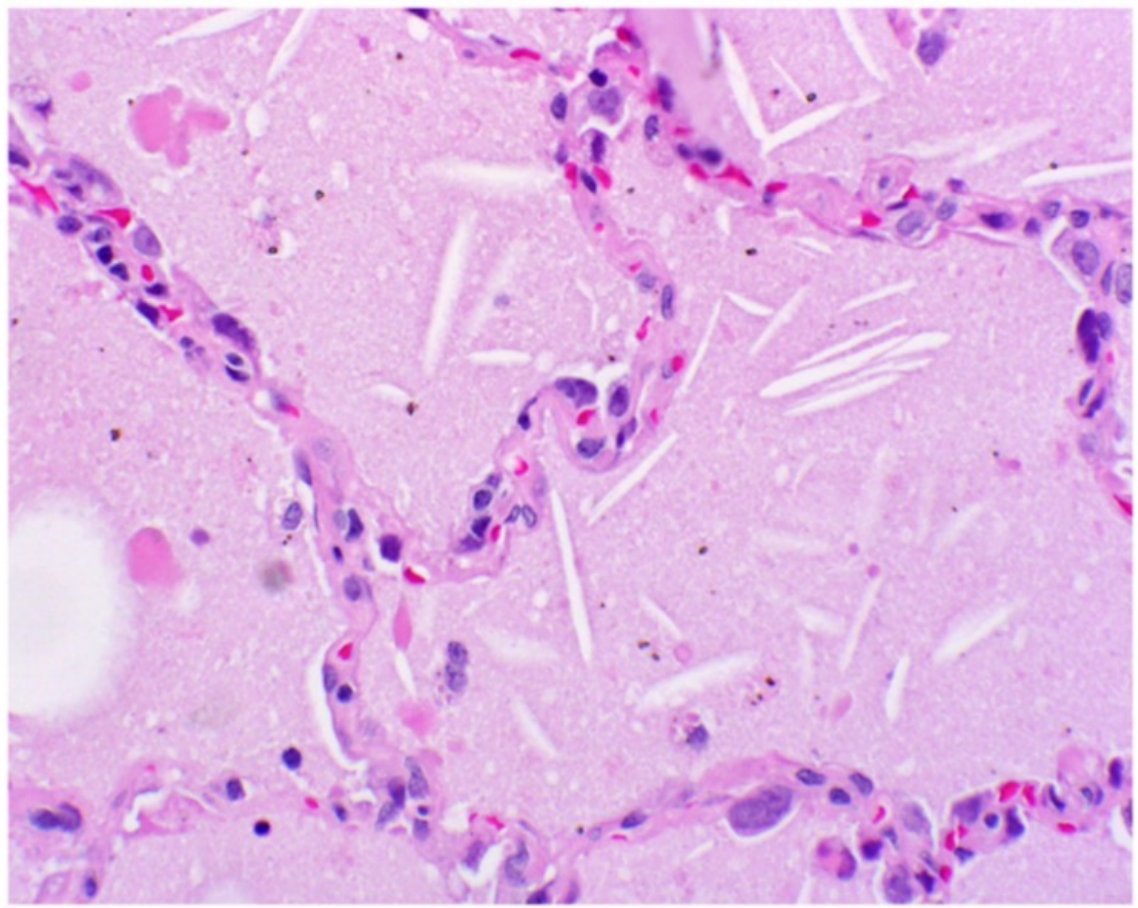
Fig.1. Chest roentgenogram of this patient showing ground glass opacities in all lung fields and minor pneumothorax in the bilateral apexes.

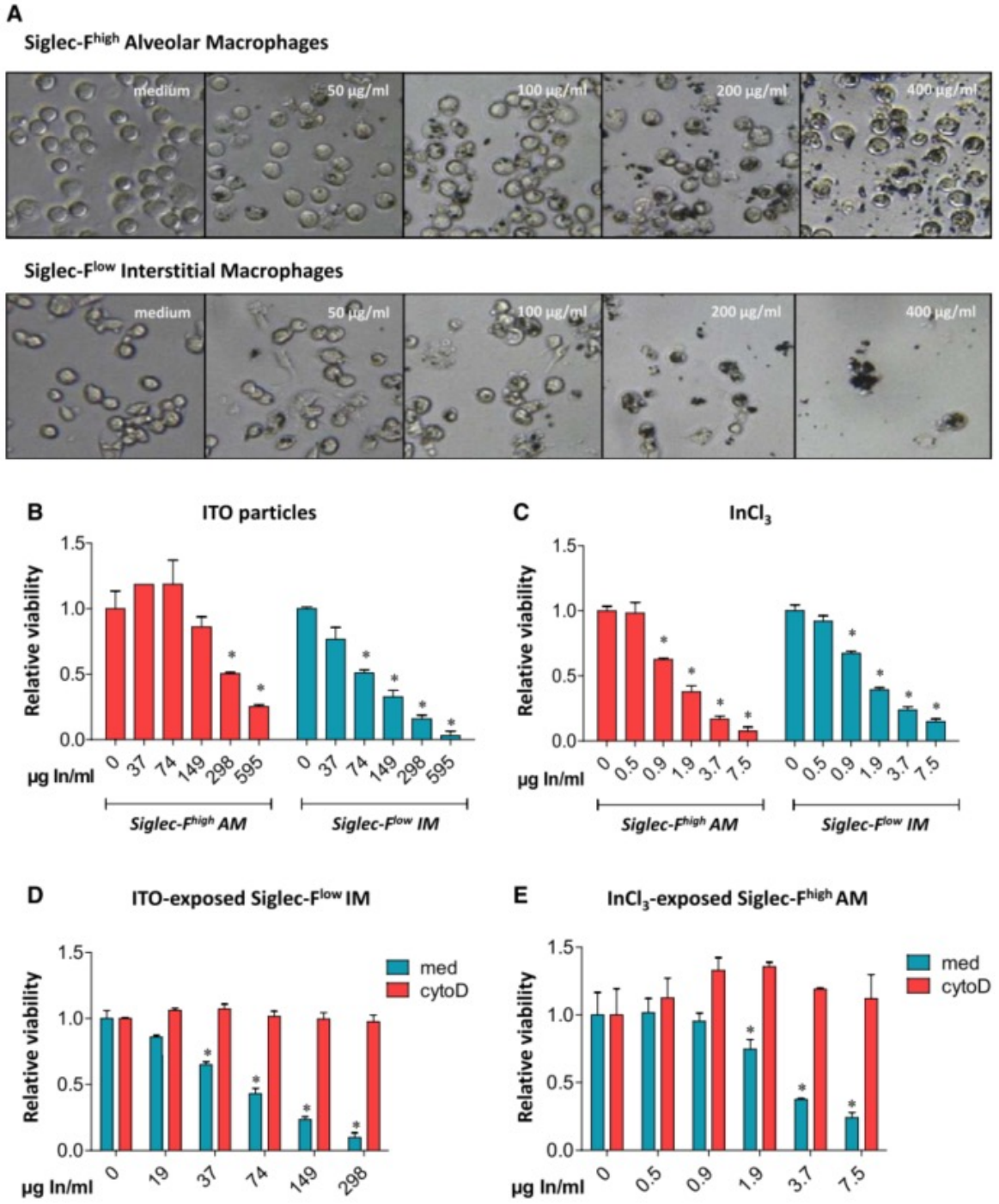
Case Report

Pulmonary Alveolar Proteinosis in Workers at an Indium Processing Facility

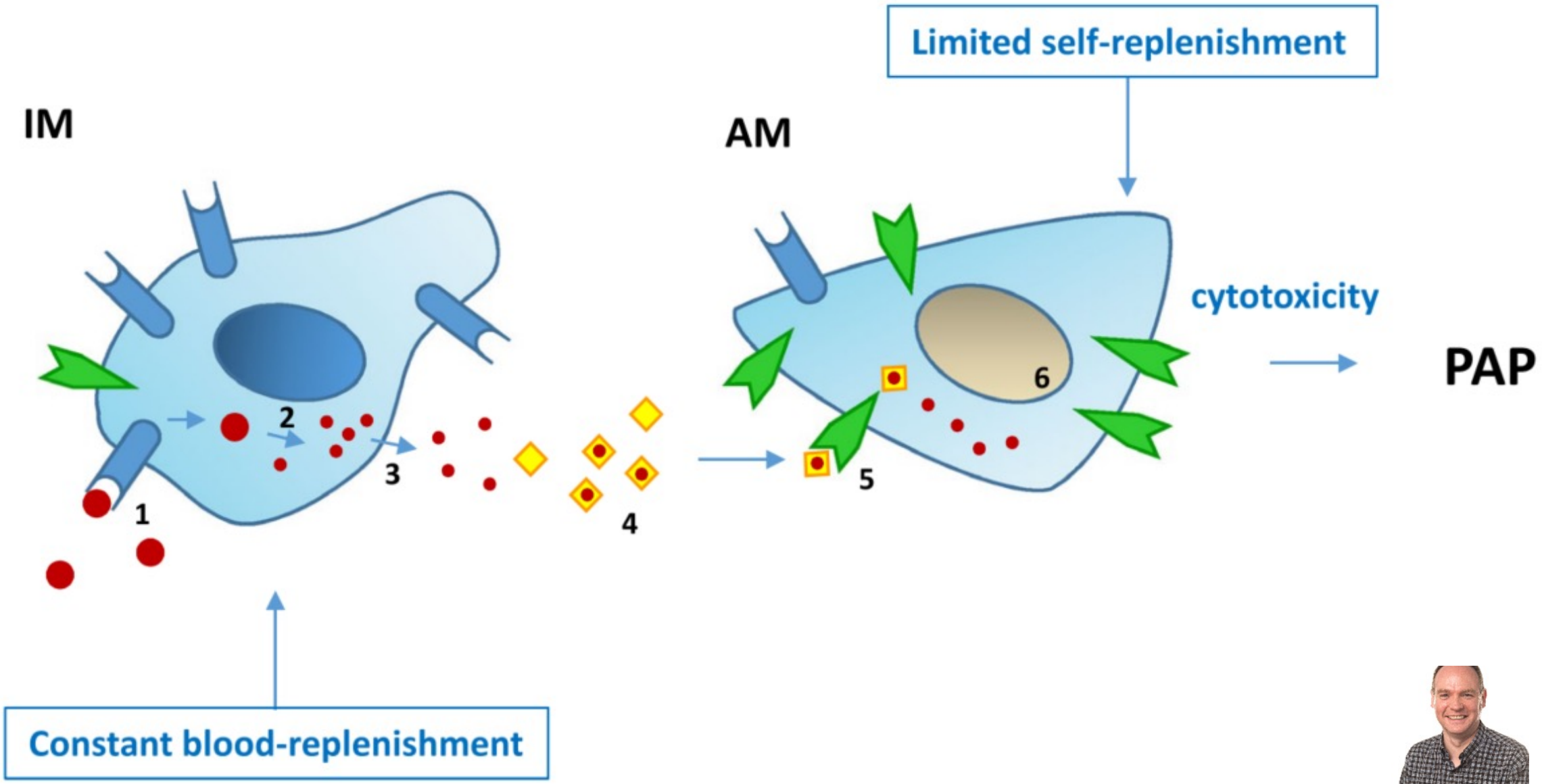
Kristin J. Cummings[1], Walter E. Donat[2], David B. Ettensohn[2], Victor L. Roggli[3], Peter Ingram[3], and Kathleen Kreiss[1]

[1]Division of Respiratory Disease Studies, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Morgantown, West Virginia; [2]Department of Medicine, Warren Alpert Medical School of Brown University, Providence, Rhode Island; and [3]Department of Pathology, Duke University Medical Center, Durham, North Carolina



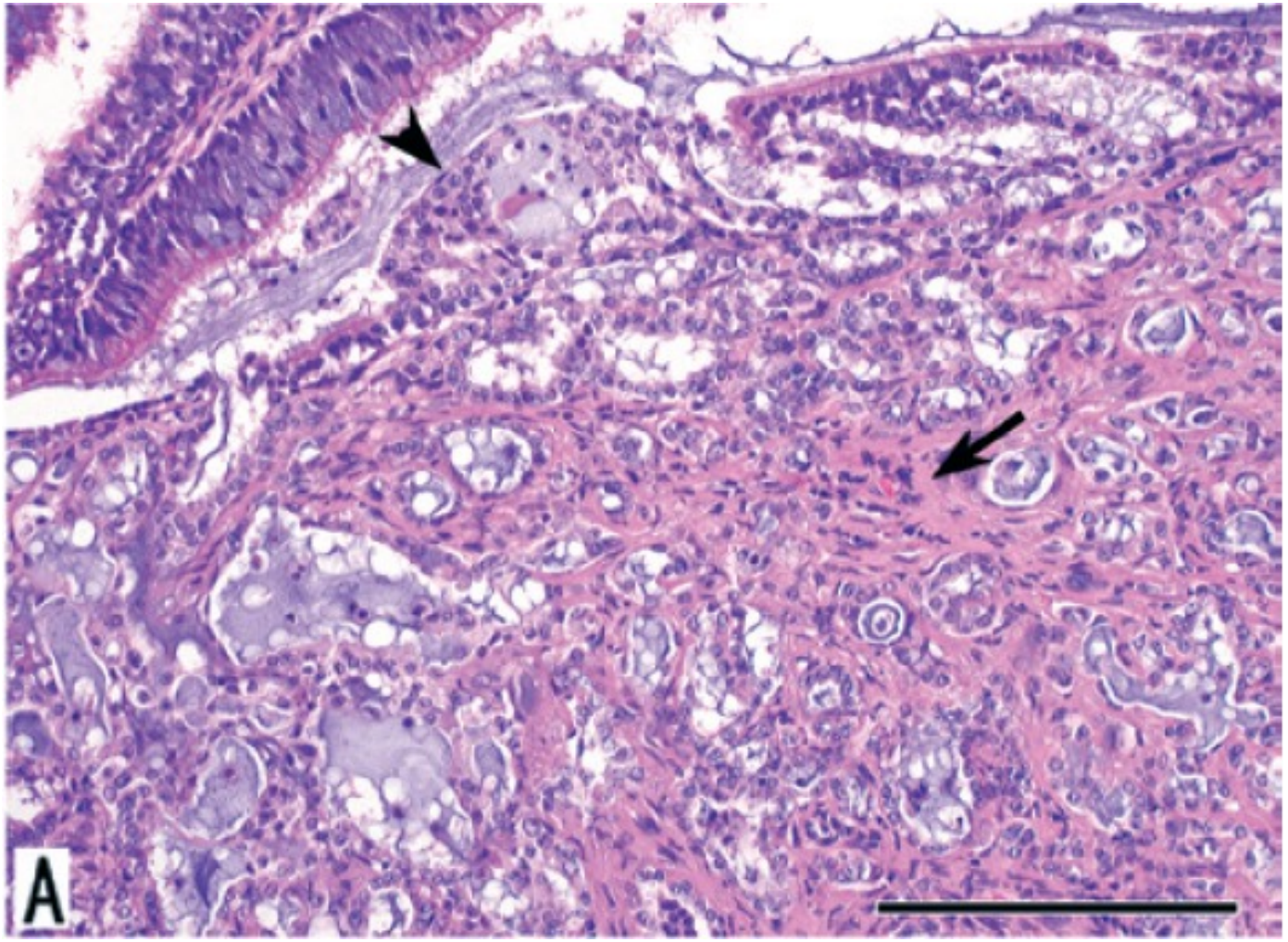


Huaux et al., 2018



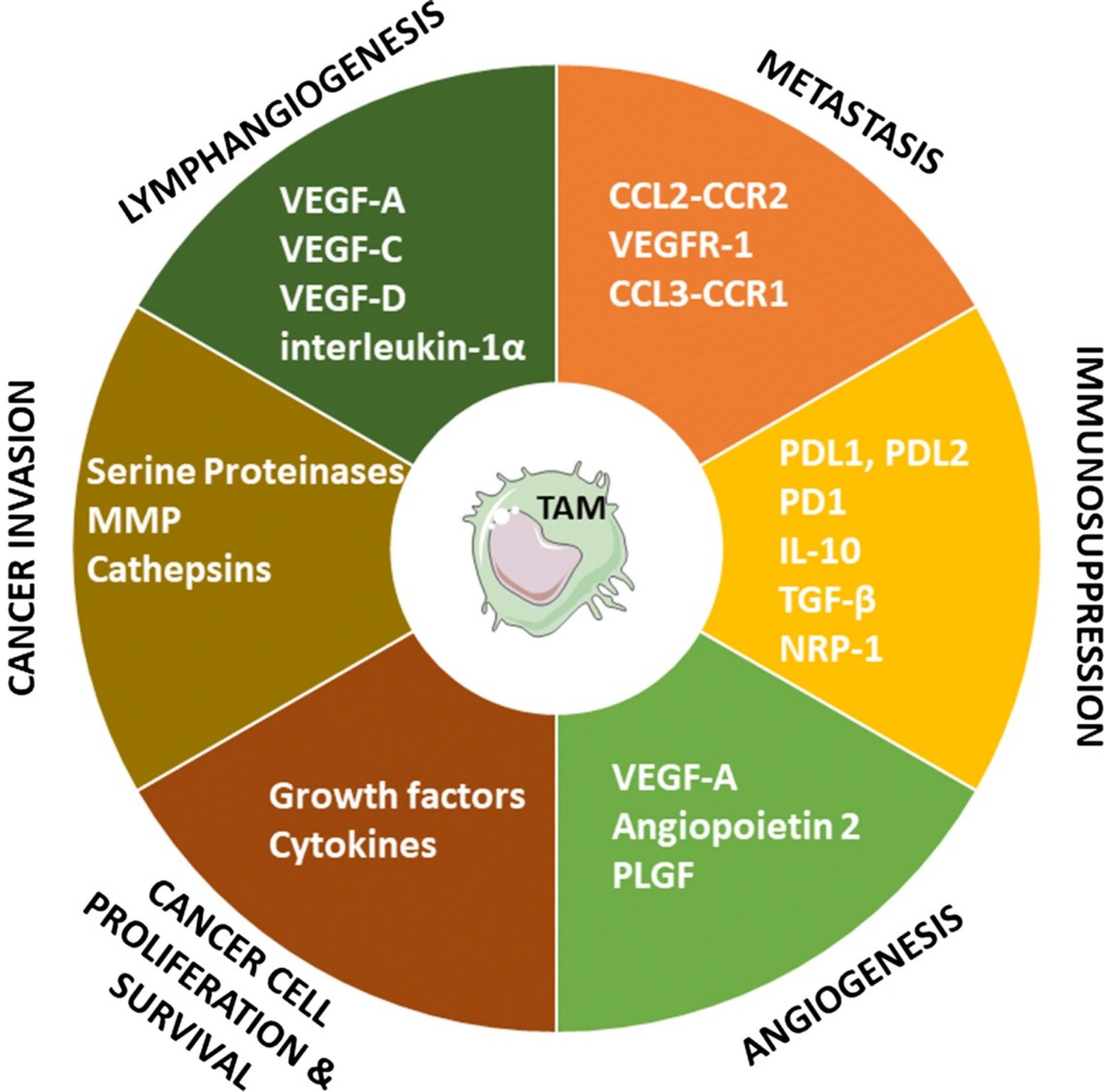
Huaux et al., 2018

≥ 0.01 mg/m³ ITO; 104 weeks



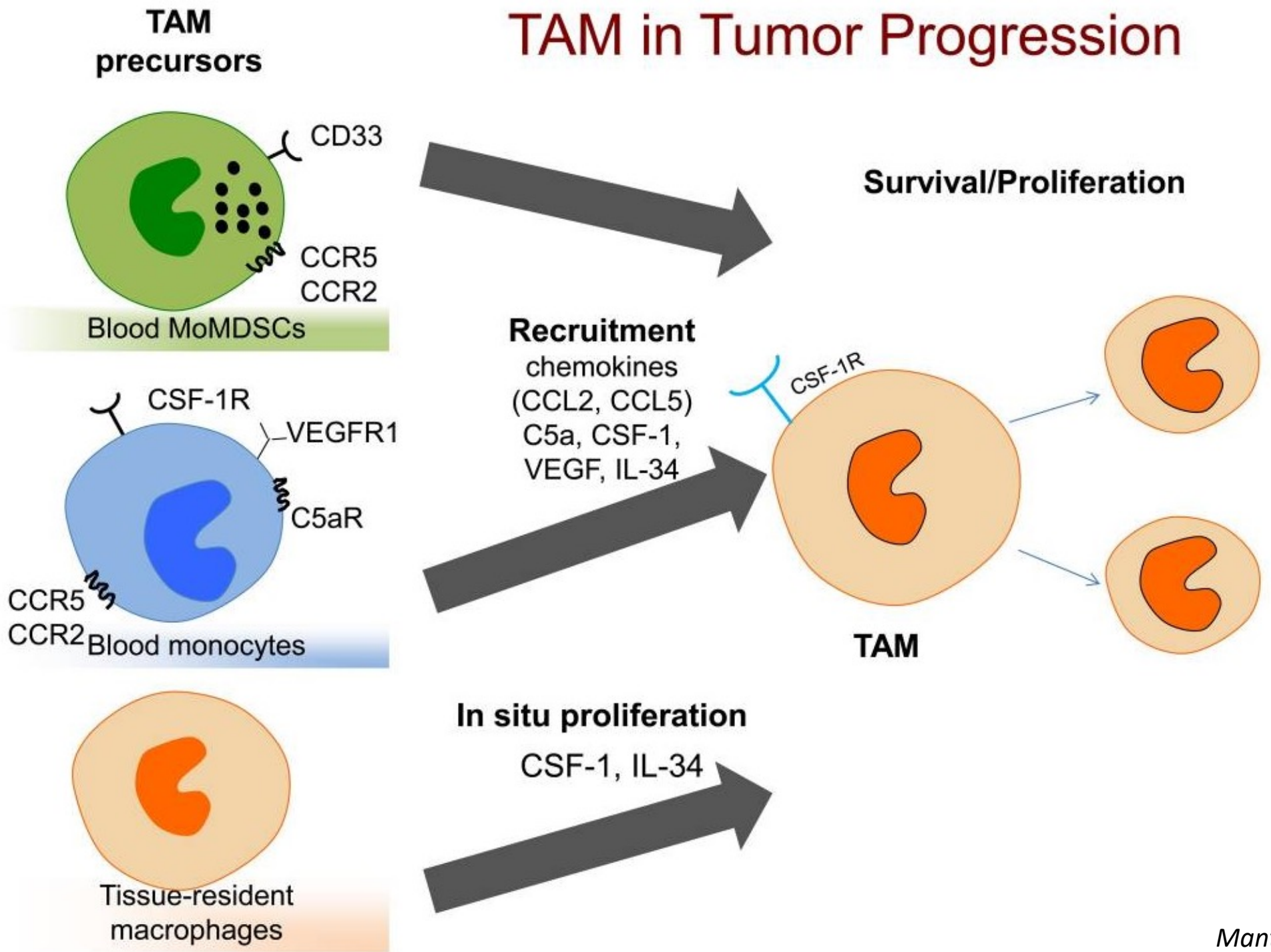
Nagano et al., 2011

tumor-associated macrophages (TAMs)

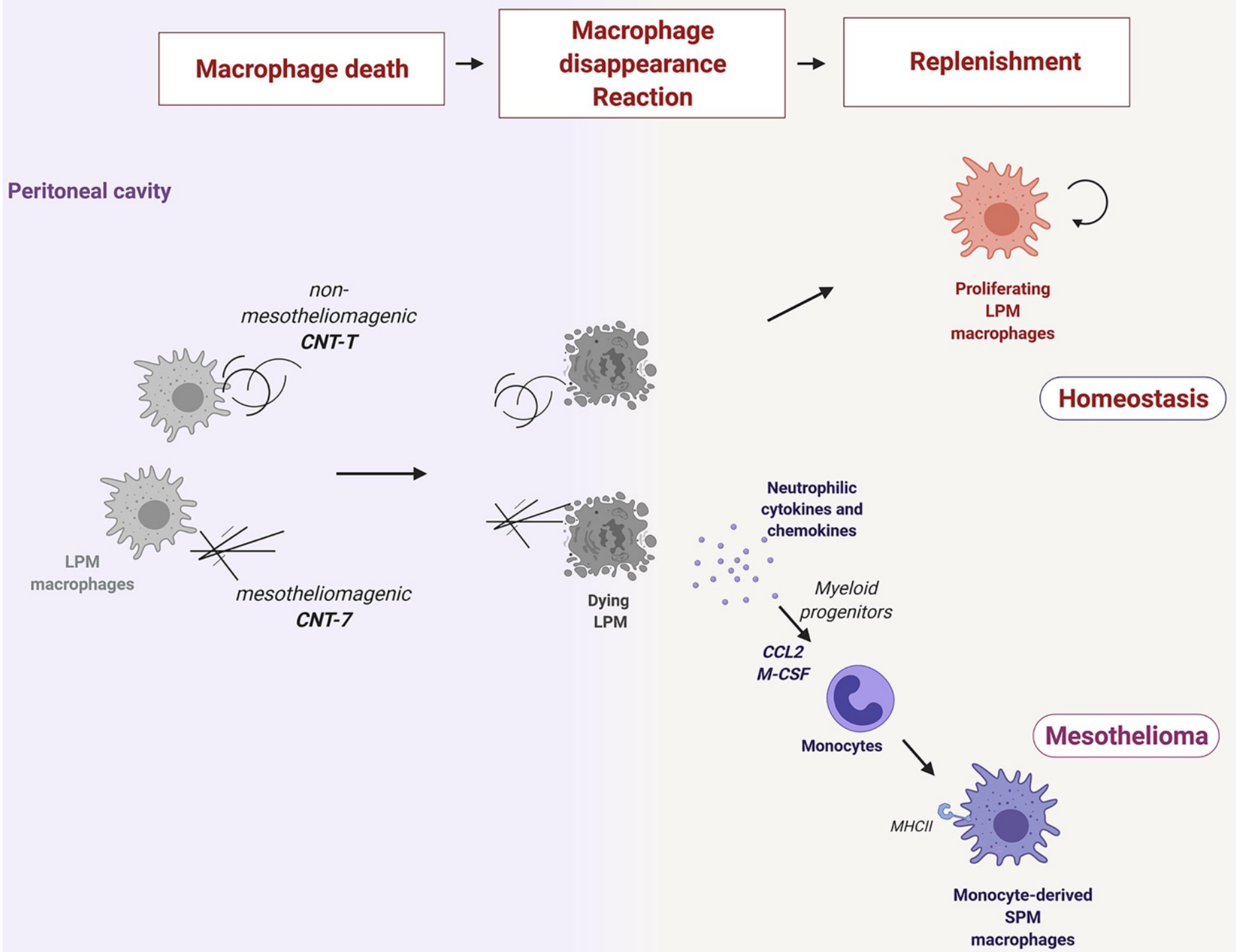


Prenen & Mazzone, 2019

TAM in Tumor Progression



Mantovani et al., 2017



Orsi et al., 2021

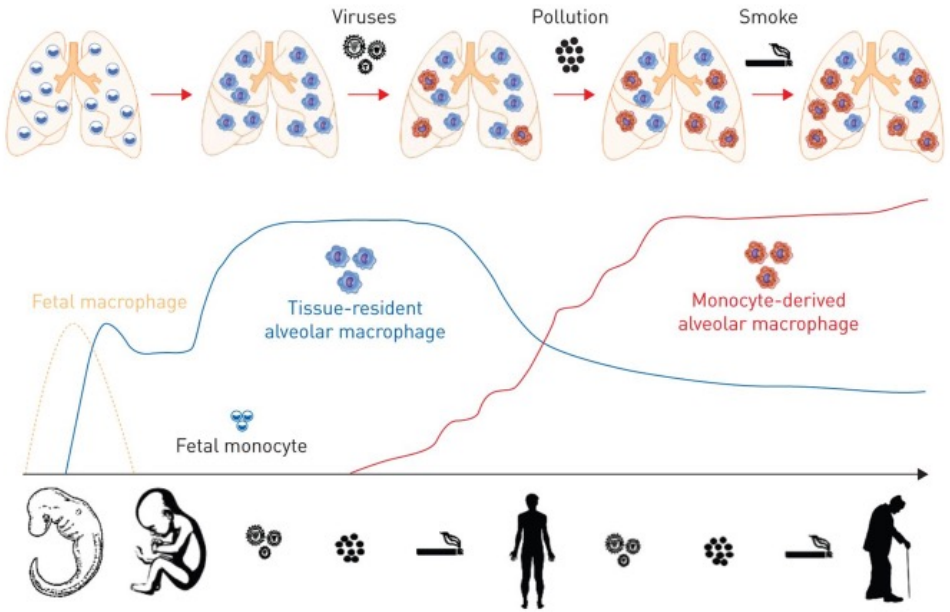
Implications for (particle) toxicology paradigms

- neglected (potential) targets of toxicity :
  - increasing role of inflammation
  - macrophage sub-populations
  - TAMs and other microenvironment cells

Implications for (particle) toxicology paradigms

- neglected (potential) targets of toxicity :
  - increasing role of inflammation
  - macrophage sub-populations
  - TAMs and other microenvironment cells

- relevance of in vitro models :
  - cell lines ???
  - lung Mϕ cultures ?



Morales-Nebreda et al., 2015