
Diesel Soot Exposure Modulates Functional Differentiation and Maturation of Bone Marrow-Derived Dendritic Cells

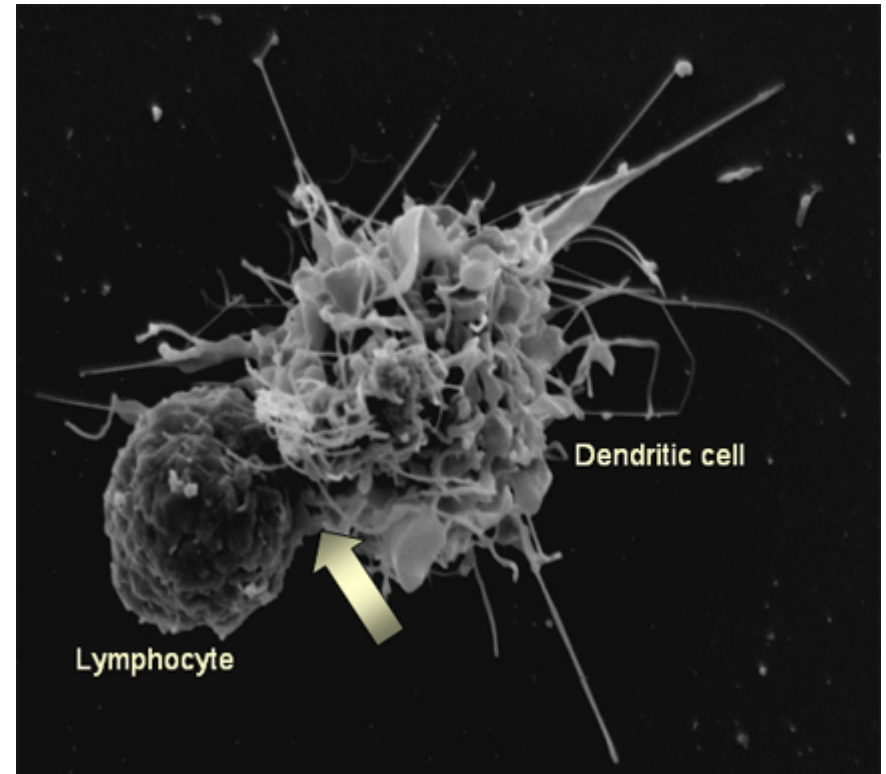
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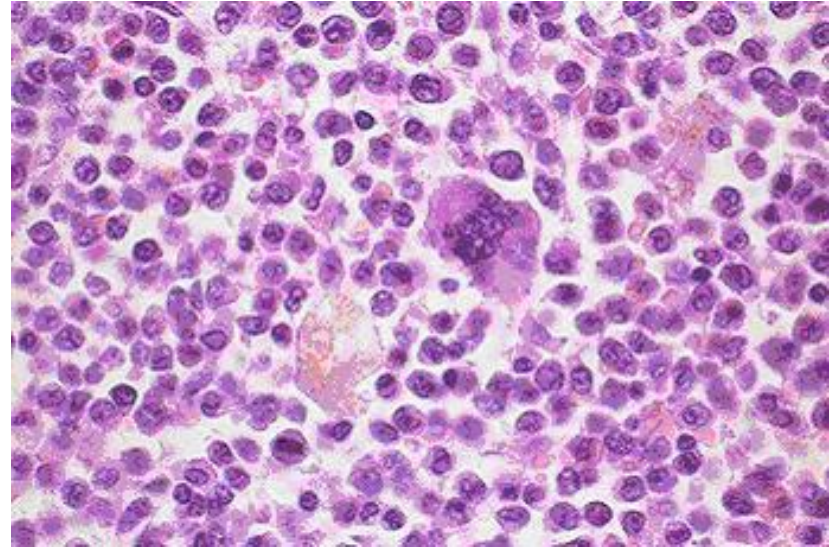
Dendritic Cells (DC)

- DC are present at sites where pathogens may enter the body, i.e. close to surfaces like skin and mucosal tissue.
- DC are often the first cells of the immune system to encounter pathogens.
- DC actively take up and process foreign matter.
- DC activate other immune cells to respond.
- DC are prime candidates for being influenced by environmental pollutants.



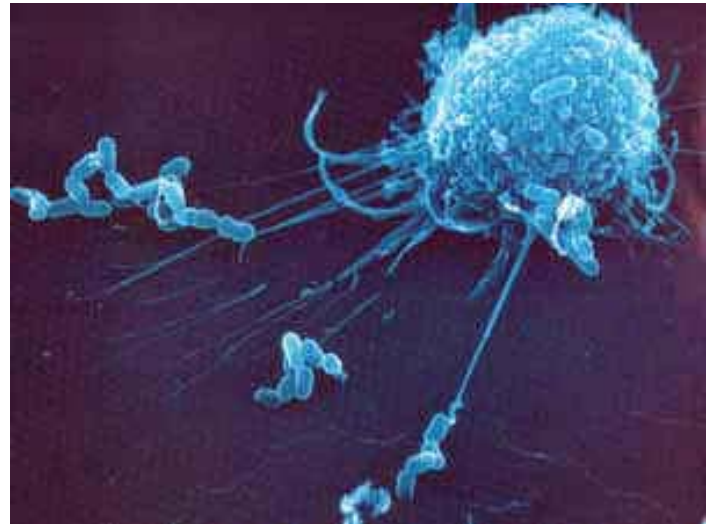
Differentiation

- DC are derived from stem cells in the bone marrow. When needed the cells travel from the bone marrow to their target organs.
- DC can be produced from bone marrow (mouse) or from blood (human) by growing cells in culture with the appropriate hormones.
- The result are immature DC, which are not yet doing anything, but are ready to go.



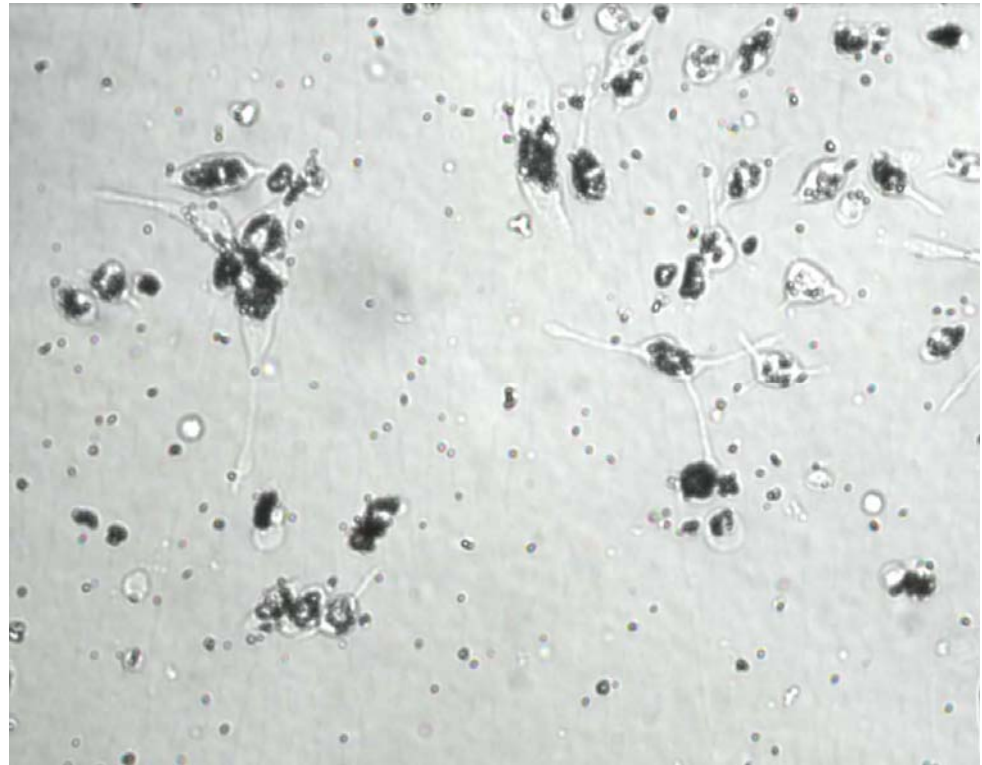
Maturation

- Immature DC get activated when they have contact to bacteria, viruses, or other pathogens. Activated DC migrate to the next lymph node.
- The mature DC which arrive in the lymph node are mature DC which are now ready to stimulate T cells.
- Maturation can also be mimicked in cell culture.



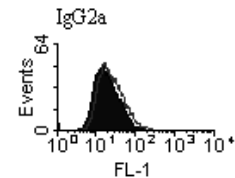
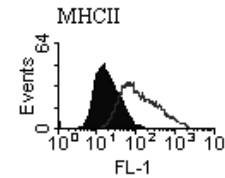
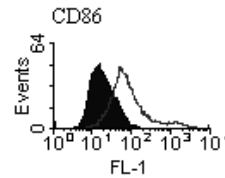
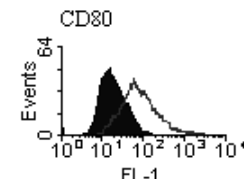
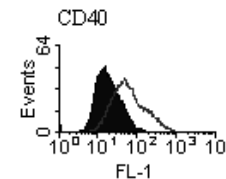
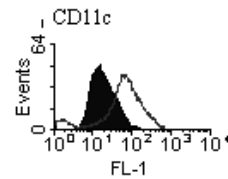
Dendritic cells and DEP

- DC were exposed to Diesel soot (Euro 3 light duty engine), carbon black (39 nm, aggregates 122 nm), graphite (1-2 μm), and Printex XE 2 (30 nm).
- The particles are not toxic at the concentrations used (40 $\mu\text{g}/\text{ml}$).
- Are there relevant parameters which indicate effects of particles on the immune system?



Differentiation of cells to immature DC

- Bone marrow cells were removed from mouse femur and cultured 10 d in presence of GM-CSF.
- Expression of the DC markers CD11c, CD40, CD80, CD86 and MHCII is induced on the surface of the cells.



CD11c

CD14

w/o

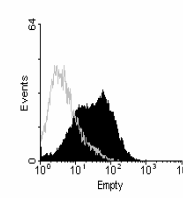
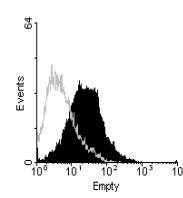
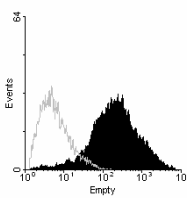
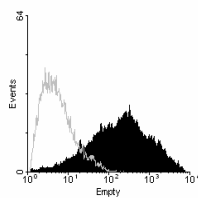
+LPS 48h

w/o

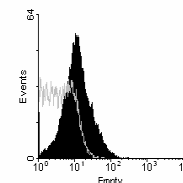
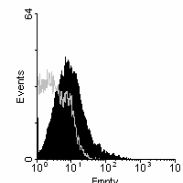
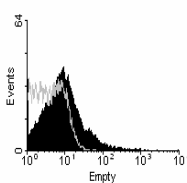
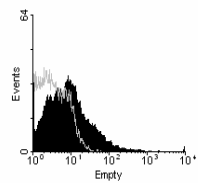
+LPS 48h

From d0 +

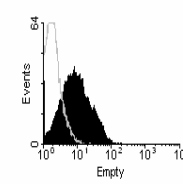
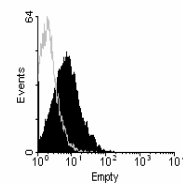
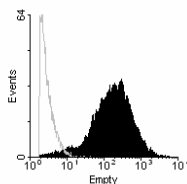
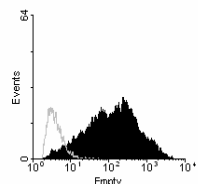
w/o



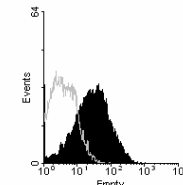
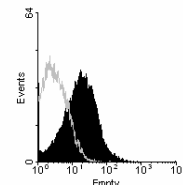
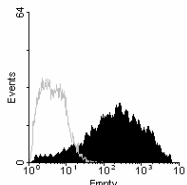
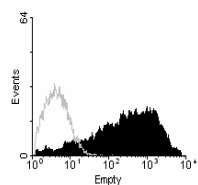
diesel-soot



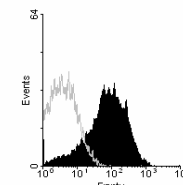
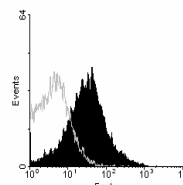
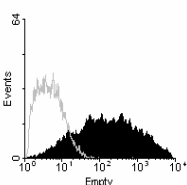
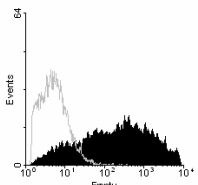
carbon black
39nm, aggregates 122nm



graphite
1-2µm



Printex XE2
30nm



CD80

CD86

w/o

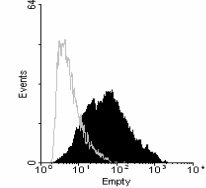
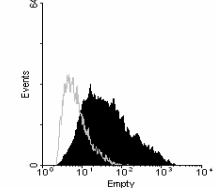
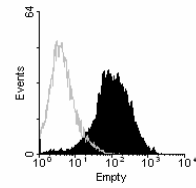
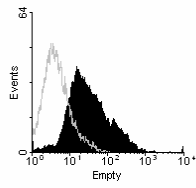
+LPS 48h

w/o

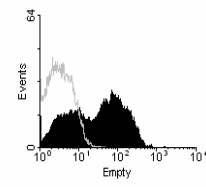
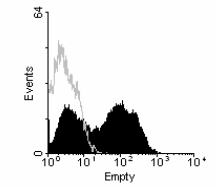
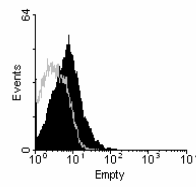
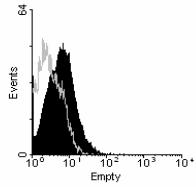
+LPS 48h

From d0 +

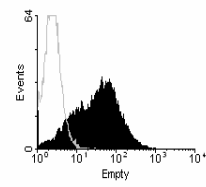
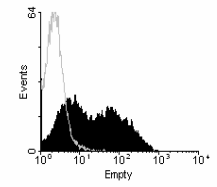
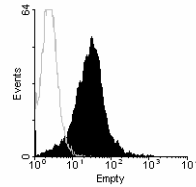
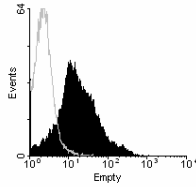
w/o



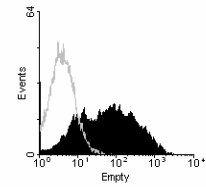
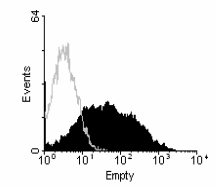
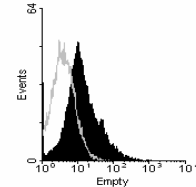
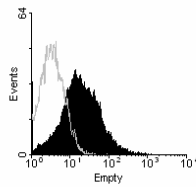
diesel-soot



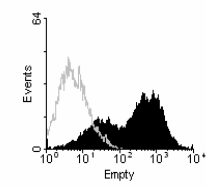
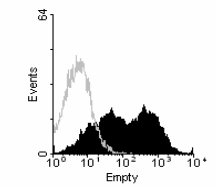
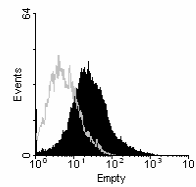
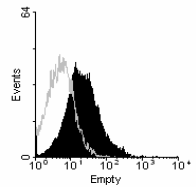
carbon black
39nm, aggregates 122nm



graphite
1-2µm

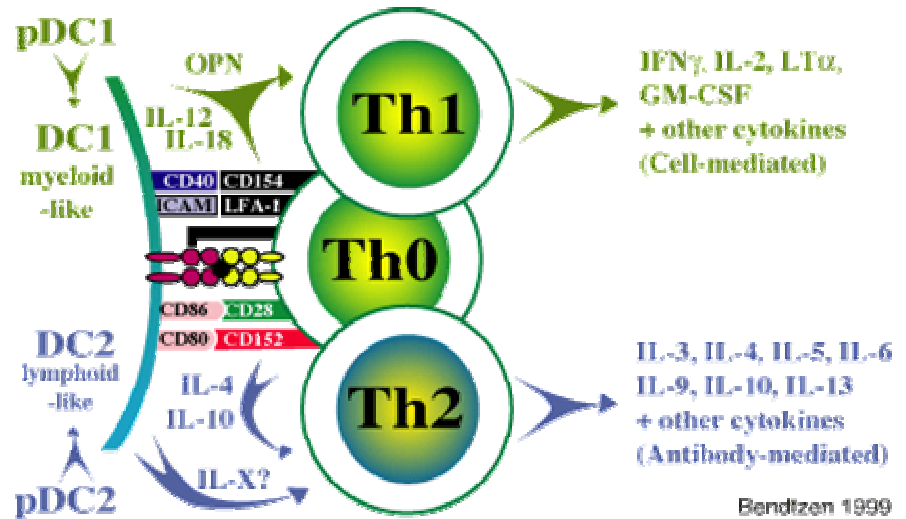


Printex XE2
30nm



CD86 - why worry?

- CD86 is a protein on the surface of activated DC.
- It delivers an important activation signal to the T cells.
- A T cell which does not get all required activation signal does not get activated a bit less !
It is turned off !
Permanently !
- It will have to be tested in mouse models whether this occurs in vivo.

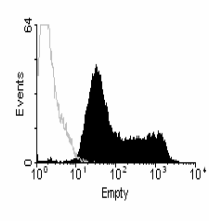
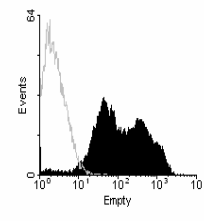
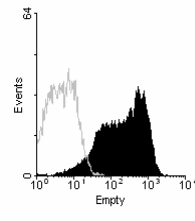
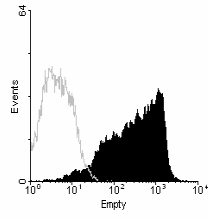
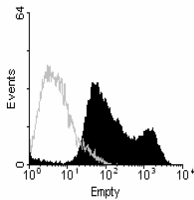
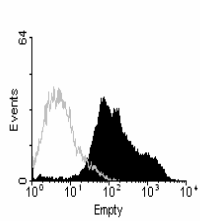


From d0 +/- LPS O_2^-

w/o

diesel-soot

carbon black



-

+

-

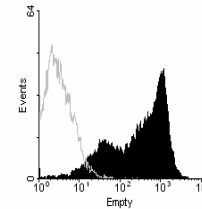
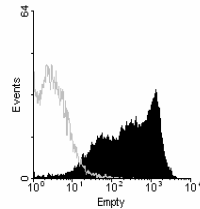
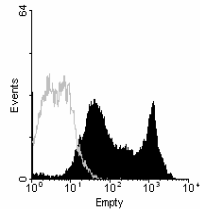
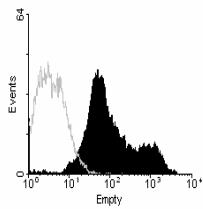
+

-

+

graphite

Printex XE2



-

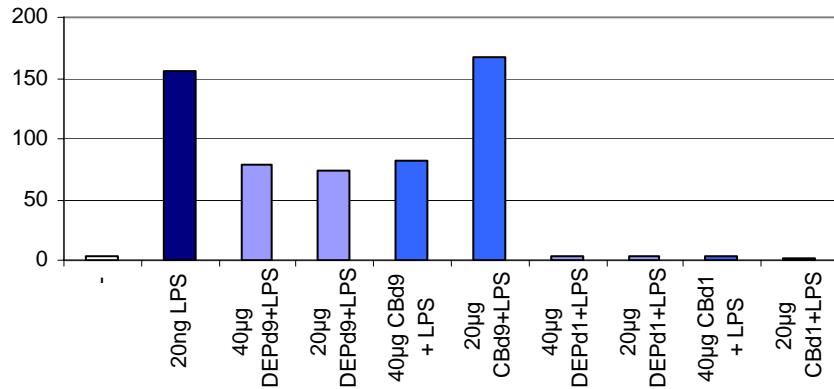
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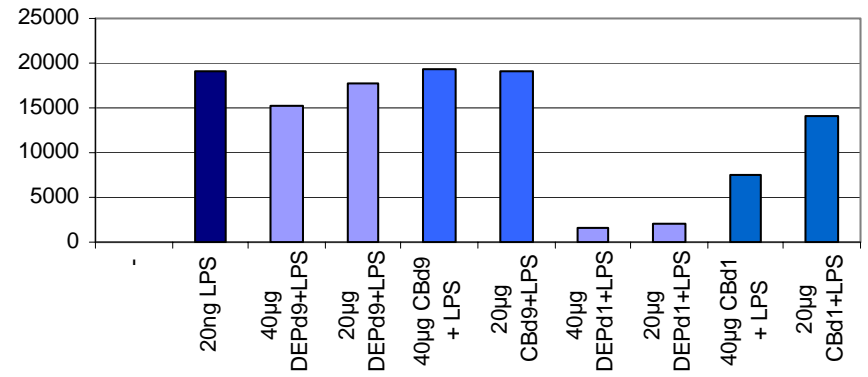
+

Immune hormones: Cytokines

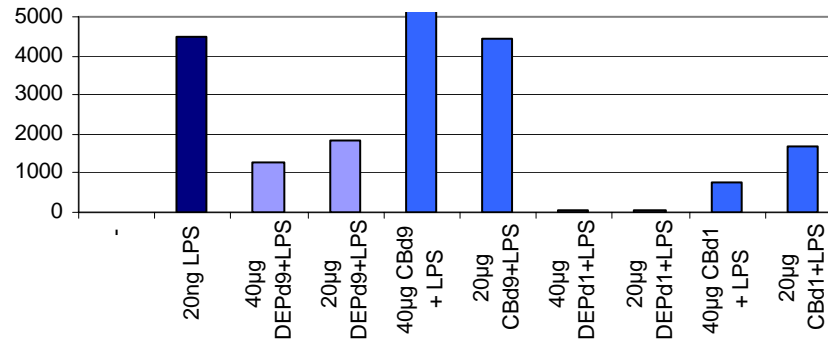
IL-10
pg/ml



IL-6
pg/ml



TNFalpha
pg/ml



Particle effects

Summary

- Diesel soot inhibits immune functions of dendritic cells in some ways (CD86, TNF-alpha) but delivers activation signals as well (superoxide anions, IL-10).
- Other nanoparticles (Printex, carbon black) have similar effects on CD86 as DEP.
- The mechanisms involved have yet to be characterized.





Our Team:

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Angela Ehard, Petra Luft

Signal transduction: Daniel Hebenstreit, Gernot Posselt, Gerald Wirsberger, Angela Schmidlechner

Support: **EU 5FP MAAPHRI**, EU 6FP NOMIRACLE, BMBF, FWF

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Heidelberg: Min Li-Weber

Leipzig: Irina Lehmann, Olf Herbarth

Rouen: **Jean-Paul Morin**

Orleans: Bruno Schnyder

Kapstadt: Frank Brombacher

Mainz: Ulrich Pöschl

Thessaloniki: **Athanasios Konstandopoulos**