Alveolar Macrophage ABCG1 Deficiency Promotes Mitochondrial Dysfunction and Pulmonary Granulomatous Inflammation

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PULMONARY SARCOIDOSIS

- Pulmonary sarcoidosis is a chronic inflammatory condition characterized by the presence of granulomas.
- Most patients enter remission.
- 20% develop fibrotic lung disease (granuloma → fibrosis).
- Morbidity and mortality are substantially increased for patients with fibrosis.

Multiwall Carbon Nanotube (MWCNT)-induced granulomatous lung inflammation
Alveolar macrophages in MWCNT-instilled mice are LIPID LADEN
Lipid metabolism in macrophages

- LDL
- LDL-R
- SREBP2
- LXR
- RXR
- LDL-R
- ABCA1
- ABCG1
- miR-33
- Apo-A1
- HDL
- Foxa2
- Cyt-c
- Caspase 3/7
- Apoptosis
- FOAM CELL
- Cytokines
- ROS
- Activated mΦ
- Ox-LDL
- TGF-β
- Fibrosis
- Phagocytosis

Activated mΦ

- FOAM CELL
- Cyt-c
- Caspase 3/7
- Apoptosis

Phagocytosis

TGF-β

Fibrosis

miR-33

Phagocytosis
Proposed mechanism of granuloma and fibrosis formation

AM engulf MWCNT

Granuloma → Cytokines

↑↑↑↑ ROS

Ox-LDL

↑ CD36 & LOX-1

↑↑↑↑ OxPLs

↑↑↑↑ miR-33

Mito. Dysfunction

Cyt. c

Apoptosis

Phagocytosis of apoptotic cells

↑↑↑↑ TGF-β → Fibrosis

↓↓↓↓ ABCG1

Foam cells

↓ HDL & lipid accumulation

Previous studies in lab
MWCNT upregulates miRNA-33 and downregulates ABCA1 and ABCG1 in AM of C57-wild type mice
ABCG1 deficiency increased the granuloma induced by MWCNT
ABCG1 deficiency increased fibrosis induced by MWCNT

Fibrosis Score

Relative Fold Change mRNA Expression

TGFβ

PDGF1

C57

ABCG1-KO

SHAM

MW CNT

SHAM MW CNT

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MW CNT

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**Proposed mechanism of granuloma and fibrosis formation**

AM engulf MWCNT

- **Granuloma**
- **Cytokines**

**ROS**
- Ox-LDL
- Ox-LDL $\uparrow$ CD36 & LOX-1

**OxPLs**

- Mito. Dysfunction
  - Cyt. c
  - Apoptosis
  - Phagocytosis of apoptotic cells
    - $\uparrow$ TGF-β → Fibrosis
  - $\uparrow$ miR-33
  - $\downarrow$ ABCG1
    - $\downarrow$ HDL & lipid accumulation
    - Foam cells
MWCNT increased Phospholipids (PC, PE) and Triglycerides in lung of C57 wild type mice
MWCNT reduced Phosphatidylserine (PS) in lung of C57 wild type mice

- PS is required for cholesterol trafficking in plasma membrane and formation of HDL
- Suggest reduction in HDL
MWCNT increase Stearoylcarnitine in lung of C57 wild type mice

Suggest deficiency in Carnitine Palmitoyl Transferase II (CPTII) and B-oxidation in mitochondria
Proposed mechanism of granuloma and fibrosis formation

AM engulf MWCNT

Granuloma → Cytokines

AM engulf MWCNT → Ox-LDL

↑ CD36 & LOX

↑ OxPLs

↑ miR-33

↑ ROS

Ox-LDL → CD36 & LOX-1

Mito. Dysfunction → Cyt. c → Apoptosis

Phagocytosis of apoptotic cells

↑ TGF-β → Fibrosis

↓ ABCG1

↓ HDL & lipid accumulation

Foam cells
MWCNT increased ROS production in BAL cells of C57 wild type mice
Proposed mechanism of granuloma and fibrosis formation

- AM engulf MWCNT
  - Granuloma → Cytokines
  - Ox-LDL
    - ↑ CD36 & LOX-1
    - OxPLs
      - ↑ miR-33
        - ↓ ABCG1
          - ↓ HDL & lipid accumulation
            - Foam cells
  - Mito. Dysfunction
    - Cyt. c
      - Apoptosis
        - Phagocytosis of apoptotic cells
          - ↑ TGF-β → Fibrosis
  - ROS
    - Ox-LDL
      - ↑ CD36 & LOX-1
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        - ↓ ABCG1
          - ↓ HDL & lipid accumulation
            - Foam cells
MWCNT reduced mitochondrial function in BAL cells of wild type mice.
Proposed mechanism of granuloma and fibrosis formation

AM engulf MWCNT

Granuloma ← Cytokines

ROS

→ Ox-LDL

→ Ox-LDL

↑ CD36 & LOX-1

↑ OxPLs

Mito. Dysfunction

↑ miR-33

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↓ HDL & lipid accumulation

Foam cells

Apoptosis

↓ TGF-β → Fibrosis

Phagocytosis of apoptotic cells
MWCNT induced apoptosis in BAL cells of wild type mice

Caspase 3/7 activity

Relative luminescence/10^3 cells

- SHAM
- MWCNT

* Indicates a significant difference.
Proposed mechanism of granuloma and fibrosis formation

AM engulf MWCNT

Granuloma ← Cytokines

ROS

Ox-LDL

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Phagocytosis of apoptotic cells

Apoptosis

Mito. Dysfunction

Cyt. c
ABCG1 deficiency promotes mitochondrial dysfunction induced by MWCNT

**Mitochondrial respiration**

- SHAM
- MWCNT

**Beta oxidation**

- SHAM
- MWCNT

* Indicates a significant difference.
• ROS production and mitochondrial dysfunction in alveolar macrophages may contribute to induction of fibrosis by MWCNT

• ABCG1 deficiency enhanced mitochondrial damage and increased fibrosis in MWCNT-induced granuloma