Role of macrophages in disease development and progression

Frank Tacke

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Disclosures Frank Tacke

• Research support (materials, funding):
  Tobira/Allergan (CVC), Noxxon (mNOX-E36), Galapagos

• Speaker/Advisory Board:
  Tobira/Allergan, Gilead, AbbVie, BMS, Boehringer, Galapagos, Intercept, Falk, Inventiva
Macrophage accumulation is a hallmark of progressive non-alcoholic steatohepatitis

Baeck C / Tacke F. Hepatology 2014
Ehling J / Tacke F. Gut 2014
Wehr A / Tacke F. J Immunol 2013
Baeck C / Tacke F. Gut 2012
Karlmark KR / Tacke F. Hepatology 2009
Tacke F / Randolph GJ. J Clin Invest 2007
Monocyte / macrophage heterogeneity in liver inflammation, fibrosis and cancer

**Origin**
homeostasis vs. inflammation

- Scott CL / Guillas M. *Nat Commun* 2016
- Wang J, Kubes P. *Cell.* 2016

**Differentiation**
microenvironmental signals shape phenotype

- Xue J / Schultze J. *Immunity* 2014
- Beattie J / Kane PM. *J Hepatol* 2016
- Bartneck M / Tacke F. *Hepatology* 2016

**Function regarding liver injury**
pro-inflammatory (can) develop into restorative macrophages

- Ramachandran P / Iredale JP. *PNAS* 2012
- Baeck C / Tacke F. *Hepatology* 2014

**Monocytes**

- Ly6C\(^{hi}\)
- Ly6C\(^{lo}\)

**Macrophages**

- „M1 polarization“
  - inflammation ↑
  - tumor ↓

- „M2 polarization“
  - inflammation ↓
  - remodelling ↑
  - tumor ↑

**Kupffer cells**
Monocytes and macrophages in liver diseases

- Acute liver injury
- NASH and fibrosis
- Immunometabolism
Cell Death triggers immune cell homing: acetaminophen injury

Acetaminophen (APAP) 7mg/ml on primary mouse hepatocytes
Role of infiltrating monocytes: acetaminophen induced acute liver injury


Role of infiltrating monocytes: acetaminophen induced acute liver injury


Monocytic and macrophage populations in experimental liver injury

intravital multiphoton-microscopy

Analyses of migration and cell-cell-interactions in real-time *in vivo*

Heymann F / Tacke F. *Hepatology* 2015
Heymann F / Tacke F. *J Vis Exp* 2015
CCR2\(^+\) inflammatory monocyte recruitment after acetaminophen overdose

- progressive accumulation of CCR2\(^+\) monocytes at 9-12h after APAP injury

Mossanen JC, Krenkel O / Tacke F. *Hepatology* 2016; 64(5):1667-1682
CCR2\(^+\) inflammatory monocyte recruitment after acetaminophen overdose

- progressive accumulation of CCR2\(^+\) monocytes at 9-12h after APAP injury

Mossanen JC, Krenkel O / Tacke F. Hepatology 2016; 64(5):1667-1682
Ccr2\(^{-/-}\) mice are protected in the early phase of acetaminophen induced liver injury

Monocyte-derived Macrophages (MoMF) Kupffer Cells (KC)

Mossanen JC, Krenkel O / Tacke F. Hepatology 2016; 64(5):1667-1682
CCR2⁺ monocyte-derived macrophages have an inflammatory phenotype

Mossanen JC, Krenkel O / Tacke F. *Hepatology* 2016; 64(5):1667-1682
Inflammatory CCR2+ macrophages in human acetaminophen acute liver failure

Mossanen JC, Krenkel O / Tacke F. Hepatology 2016; 64(5):1667-1682

similar data by Antoniades CG / Wendon J. Hepatology 2012; 56(2):735-46
Monocytes and macrophages in liver diseases

• Acute liver injury
• NASH and fibrosis
• Immunometabolism
Monocyte / macrophage subsets during regression of liver fibrosis

Krenkel O & Tacke F. Nat Rev Immunol 2017
Monocyte / macrophage subsets during regression of liver fibrosis

Krenkel O & Tacke F. Nat Rev Immunol 2017
Chemokine receptor CCR2/5-inhibitor CVC in experimental NASH and fibrosis

Mouse model of NASH (MCD)

**liver macrophages reduced**

Liver Leukocytes [%]

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**liver fibrosis reduced**

Sirius Red [%]

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Clinical trial phase 2b (ongoing)

Patients with NASH + fibrosis (n=289) enriched for co-morbidities

CVC 150mg (n=145) vs Placebo (n=144)

Liver biopsy after 1 year

CVC 150mg (n=145) vs CVC 150 (n>63) vs Placebo (n>63)

Liver biopsy after 2 years

Püngel T, Krenkel O, Tacke F. EASL 2016

NCT02217475; EudraCT number 2014-003164-21; Sponsor: Tobira / Allergan
Chemokine receptor CCR2/5-inhibitor CVC in experimental NASH and fibrosis

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clinical trial phase 2b (ongoing)

patients with NASH + fibrosis (n=289) enriched for co-morbidities

- CVC 150mg (n=145)
- Placebo (n=144)

liver biopsy after 1 year

interim analysis after 1 year treatment:
- 126 + 126 sufficient paired biopsies
- baseline characteristics:
  - 33% F1, 29% F2, 38% F3 fibrosis
  - 52% type 2 diabetes, BMI ~34 kg/m²

Sanyal A et al. #LB-1, AASLD 2016

Sponsor: Tobira / Allergan
Chemokine receptor CCR2/5-inhibitor CVC in patients with NASH and fibrosis

Steatohepatitis-Score

Placebo (N=144)  CVC (N=145)

0%  5%  10%  15%  20%  25%
19%  16%

≥2-point Improvement in NAS AND No Worsening of Fibrosis

Fibrosis-Score

0%  5%  10%  15%  20%  25%
10%  20%

Improvement in Fibrosis Stage AND No Worsening of NASH

P = 0.0234

NASH resolution: 8% vs. 6% (n.s.)

Sanyal AJ, et al. AASLD 2016, #LB-1
Chemokine receptor CCR2/5-inhibitor CVC in patients with NASH and fibrosis

Response by Baseline Fibrosis Stage (mITT)

Sanyal AJ, et al. AASLD 2016, #LB-1
Monocyte / macrophage subsets during regression of liver fibrosis

Can we therapeutically provoke this phenotypic switch?

- **Inflammatory** Ly6C\textsuperscript{high} monocyte
- **Fibrogenic** Ly6C\textsuperscript{+} macrophage
- **Restorative** Ly6C\textsuperscript{low} macrophage

- PDGF, TGF\(\beta\), TNF, IL-1\(\beta\)
- TRAIL, MMP9/12/13

- Hepatic stellate cell (HSC)
- Activated HSC (myofibroblast)
- Reverted HSC

- Extracellular matrix (ECM)

References:
- Krenkel O & Tacke F. *Nat Rev Immunol* 2017
Targeting macrophages in liver inflammation and fibrosis

Microbubbles  Liposomes  Polymers

CT+Seg.  

CT+FMT

Liver

Ergen C / Lammers T / Tacke F. Biomaterials 2017
Targeting macrophages in liver inflammation: Drug delivery systems

Liposomes i.v.

blue: Kupffer cells

Microbubbles

Kupffer cells

Monocyte-derived macrophages

Liposomes

Polymers

Ergen C / Lammers T / Tacke F. Biomaterials 2017
Targeting macrophages in liver inflammation: *Proof-of-concept* in fibrosis

Dexamethasone-loaded Liposomes

Bartneck M / Tacke F, *Nanomedicine* 2014
Bartneck M / Tacke F, *Biomaterials* 2015
Topuz F / Tacke F, *Biomacromolecules* 2017
Monocytes and macrophages in liver diseases

- Acute liver injury
- NASH and fibrosis
- Immunometabolism
Immunometabolism 1: Integration of metabolic signals by macrophages

Immunometabolism 2: Adaptation of cellular metabolism by macrophages

Manifold potential targets...
- PPAR α / γ / δ
- ASK1

Macrophage metabolism upon activation

Macrophage metabolism in homeostasis

- NF-κB activation
- glycolysis
- ROS and NO production
- distinct transcription factors
- inflammasome formation
- cytokine production

Krenkel O & Tacke F. Seminars Liver Disease 2017 (in press)
Thank you!

Tacke Lab
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Tobias Püngel
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Carmen Tag

collaborators Aachen
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Ralf Weiskirchen
Ulf Neumann

collaborators
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Florent Ginhoux
Steffen Jung
Jo van Ginderachter
Gwen Randolph

Funding
Industry (Noxxon, Tobira/Allergan)
Role of macrophages in disease development and progression of NASH

- **Monocyte and macrophage subsets** impact inflammation, hepatocyte injury, hepatic stellate cell activation, angiogenesis, but also resolution of injury, in mice and men

- Hepatic **macrophage heterogeneity** in includes origin, differentiation/ polarization, immunological properties and functions in disease progression/regression

- Therapeutic application of the **CCR2/CCR5 inhibitor CVC** in mice ameliorates steatohepatitis and fibrosis without impairing tissue repair, supporting the therapeutic potential in patients with NASH

- **Important lines of research** in the field: regulation and balance of pro- and antiinflammatory subsets, novel **imaging** approaches to dissect immune cell subsets, immune mechanisms in transition from chronic inflammation to **cancer**, targeting mechanisms by **nanoparticles**, **translation** into clinics (biomarkers + therapy)