

## NASH Pathogenesis

### Role of Cell Death and Sterile Inflammation

#### STOPNASH SYMPOSIUM

Ariel Feldstein, M.D.  
Professor of Pediatrics  
Chief, Division of Pediatric Gastroenterology  
Hepatology and Nutrition University of  
California San Diego



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## Disclosures

Co-inventor on pending and issued patents filed by the Cleveland Clinic and UCSD that refer to the use of biomarkers in fatty liver disorders.

And

Scientific Advisory Board: Gilead, Takeda, Mitsubishi-Tanabe, Raptor, Conatus

And

My presentation does not include discussion of off-label or investigational use

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## Outline

- **Pathogenic Pathways**
  - Hepatocyte cell death in NASH progression
  - Cell death - sterile inflammation loop
  - NLRP3 Inflammasome as driver of Inflammation and fibrosis
- **Summary and Conclusions**

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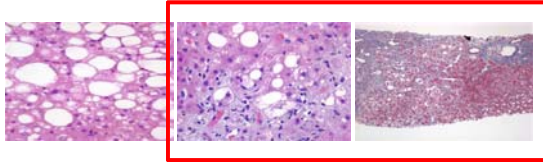
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## Non-Alcoholic Fatty Liver Disease (NAFLD)

### • Spectrum of disease

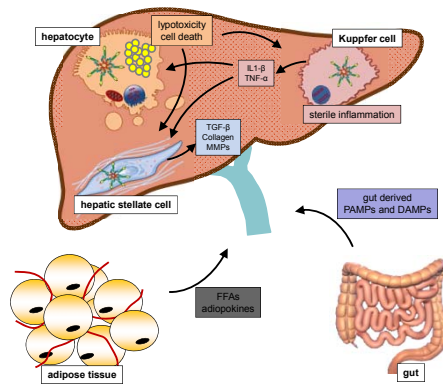
- NAFL: fatty liver (steatosis)
- NASH: steatosis + inflammation + liver injury
- Fibrotic NASH: steatosis + inflammation + liver injury + fibrosis



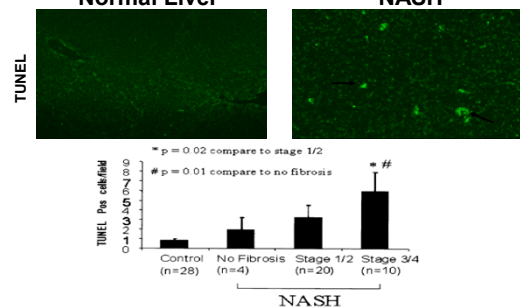
Angulo P et al. N Engl J Med 2002;346:1221-31

Angulo P et al. Gastroenterology. 2015 Aug;149(2):389-397

**NAFLD Pathogenesis:** complex interaction and crosstalk between environmental factors, host genetics and gut microflora



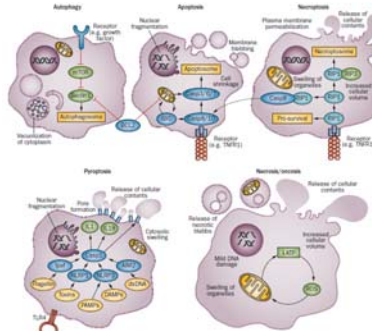
## Hepatocyte Cell Death is a Prominent Feature of Human NASH



Feldstein AE.....Gores GJ. Gastroenterology 2003;125:437-443

## Hepatocyte Cell Death

### Expanding View



Wree A.....Feldstein AE. Nature Reviews Gastroenterology and Hepatology, 2013

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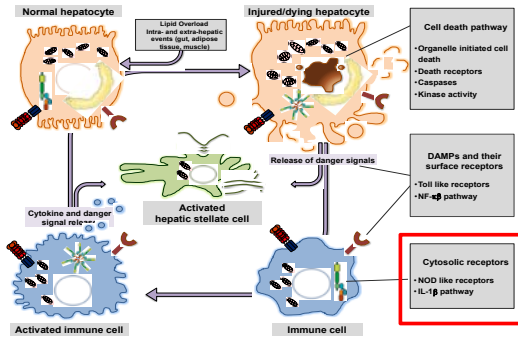
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## Cell Death and Sterile Inflammation Loop in NASH




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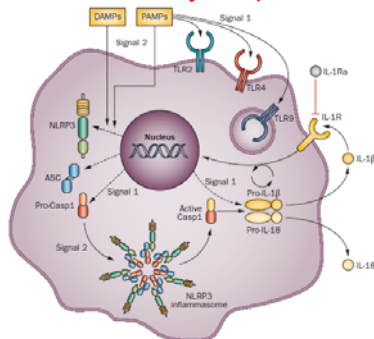
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## NLRP3 Inflammasome

### Driver of Inflammatory Response in NASH




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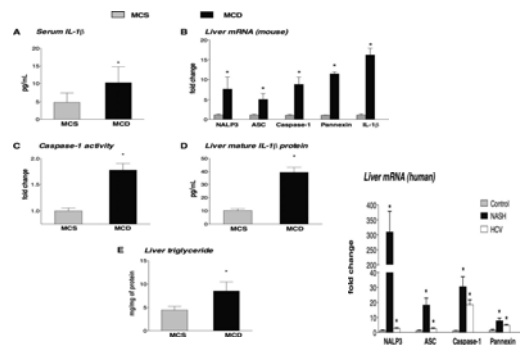
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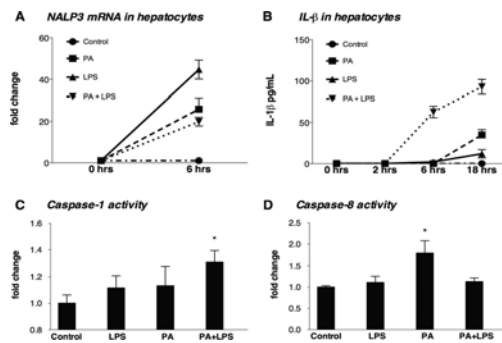
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### Experimental and Human NASH are Associated with NLRP3 Inflammasome activation in the liver

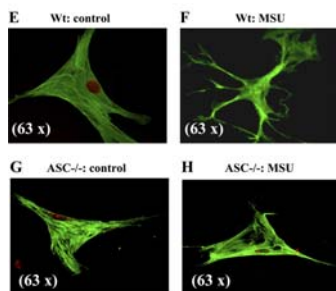


Csák et al. HEPATOLOGY 2011;54:133-144

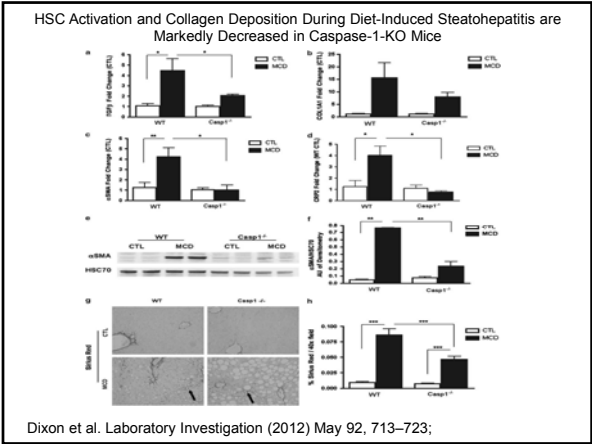
### Hepatocytes Express NLR Components and Palmitic Acid and LPS Exposure Results in Caspase 1 Activation and IL-1 $\beta$ Production



### NLRP3-inflammasome Activates Hepatic Stellate Cells



Watanabe et al. Am J Physiol Gastrointest Liver Physiol 2009




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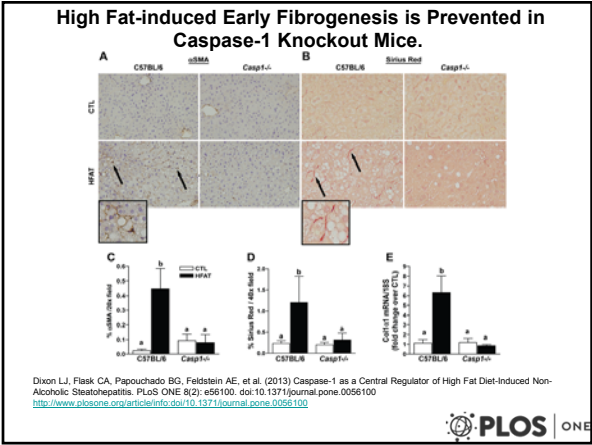
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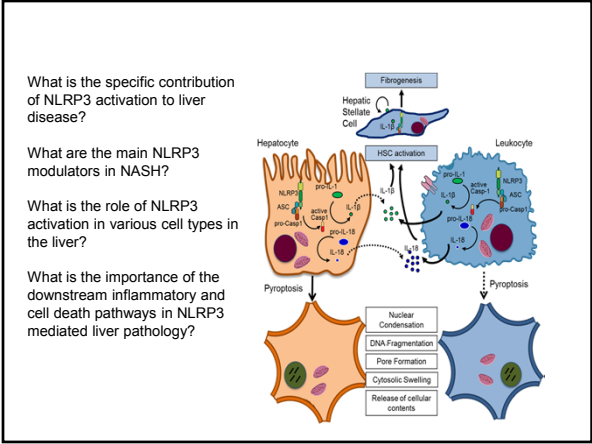
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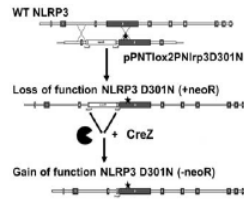
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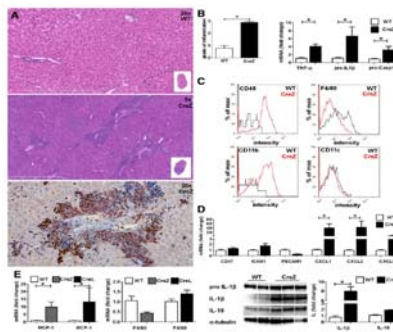
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## Development of NLPR3 Knockin Mice

Model Name	Cre recombinase	NLRP3 expression	Constitutive/Inducible
<i>Nlrp3<sup>fl</sup>/Cre<sup>L</sup></i>	LRAT – Lecithin:retinol acyltransferase	Hepatic Stellate Cells	Constitutive
<i>Nlrp3<sup>fl</sup>/Cre<sup>L</sup></i>	LysM – Lysozyme	Myeloid cells	Constitutive
<i>Nlrp3<sup>fl</sup>/Cre<sup>A</sup></i>	Alb – Albumin	Hepatocytes	Constitutive
<i>Nlrp3<sup>fl</sup>/Cre<sup>T</sup></i>	ERT – Estrogen Receptor	Universal	Tamoxifen-induced

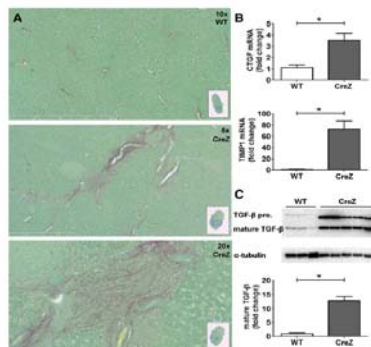


## NLRP3 Activation Leads to Severe Liver Inflammation



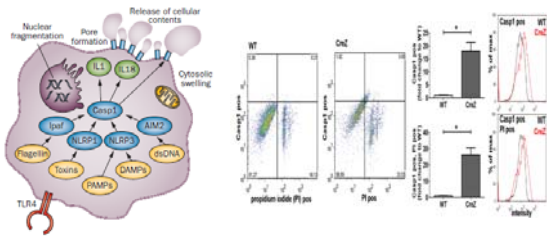
Wree et al. Hepatology 2014 Mar;59(3):898-910

## NLRP3 Activation Leads to HSC Activation and Collagen Deposition



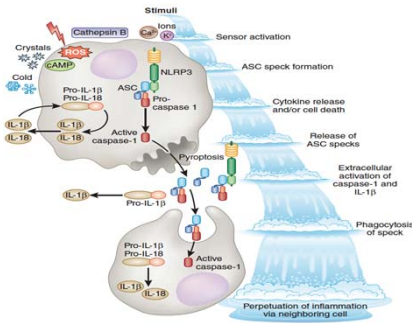
Wree et al. Hepatology 2014 Mar;59(3):898-910

## NLRP3 Activation Leads to Hepatocyte Pyroptosis



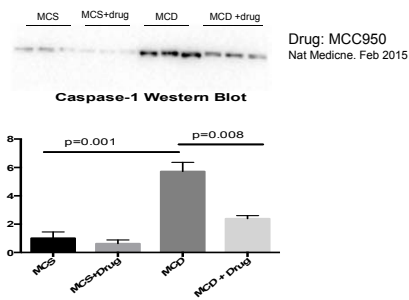
Wree et al. Hepatology 2014 Mar;59(3):898-910

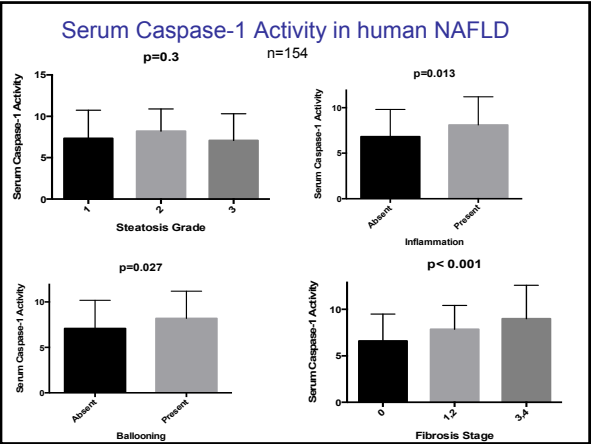
## Pyroptosis and Amplification of Inflammasome Response



Broderick et al. Nat Immunol. 2014 Aug;15(8):698-700.

## Serum Caspase-1 levels are Increased in NASH mouse model and are modulated by NLRP3 Inflammasome






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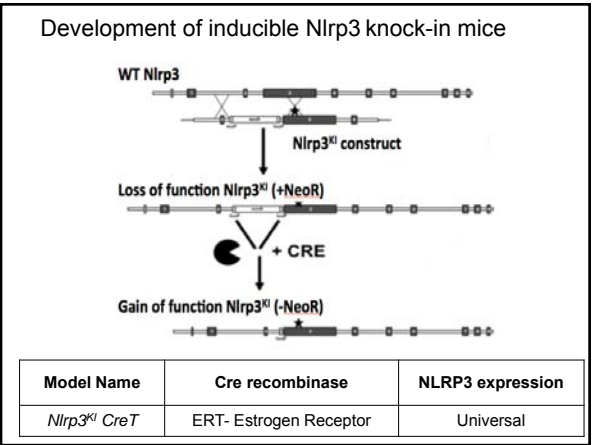
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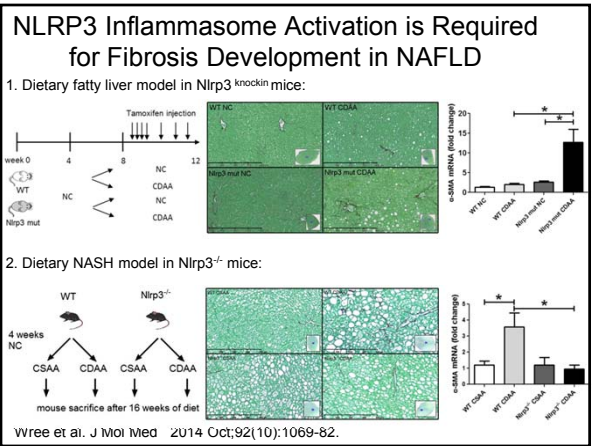
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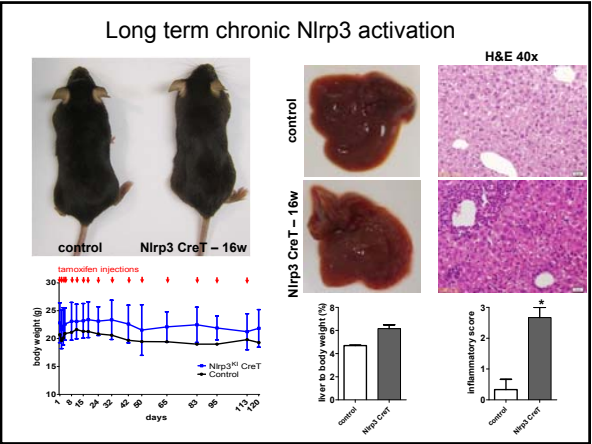
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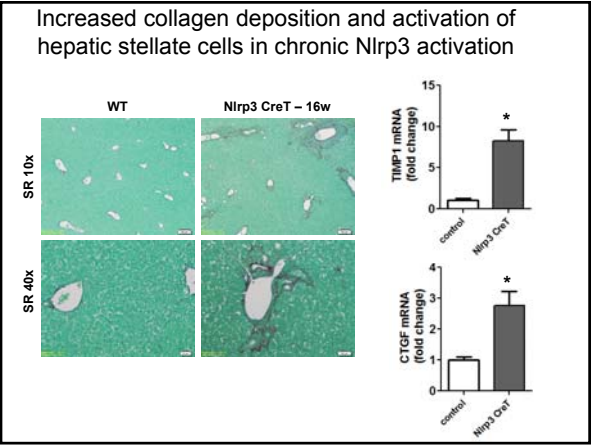
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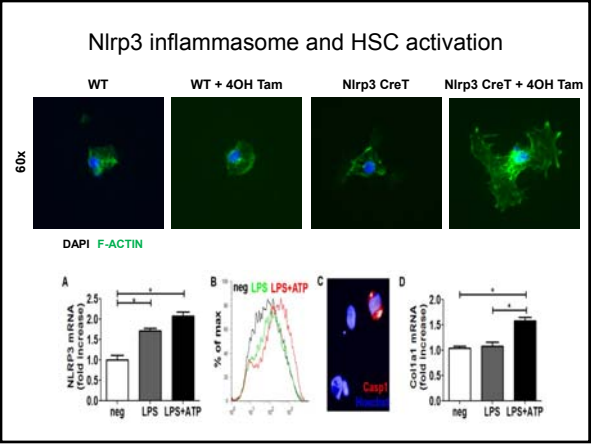
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## Summary / Conclusion

- NAFLD pathogenesis involves a complex interaction between environmental factors, host genetics and gut microflora and depends on both intrahepatic and extrahepatic events
- Hepatocyte cell death and sterile inflammation may result in a feed-forward self-perpetuating loop that triggers liver damage and fibrosis
- NLRP3 Inflammasome is a key component of this loop
- Studies using constitutively activated NLRP3 demonstrated that NLRP3 is not only required for hepatic inflammation and fibrosis, but NLRP3 activation is sufficient for hepatic inflammation and fibrosis
- Future studies to better identify the key driver of NLRP3 activation, the cell specificity and the importance of various downstream pathways in the development of liver pathology and in particular liver fibrosis during NASH development may result in novel therapies

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### Collaborators

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| • Stanley Hazen (CC)                | • Mathew Cooper (Univ. of Queensland) |
| • Thomas McIntyre (CC)              | • Rohit Kohli (Univ. of Cincinnati)   |
| • Maurizio Parola (Univ. of Torino) | • Sonia Caprio (Yale University)      |
| • Laura Nagy (CC)                   | • Susan Fisher-Hoch (UT Houston)      |
| • Leon Adams (Perth, Australia)     | • Michael Fallon (UT Houston)         |
| • Jonathan Smith (CC)               | • Santiago Horgan (UCSD)              |
| • Valerio Nobili (Rome, Italy)      | • Rohit Loomba (UCSD)                 |
| • Marco Arrese (Santiago, Chile)    | • Ekihiro Seki (UCSD)                 |
| • Craig McClain (Louisville)        | • Hal Hoffman (UCSD)                  |
| • Chris Ramsden (NIAAA)             | • Vivian Hook (UCSD)                  |
|                                     | • Michael Karin (UCSD)                |

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