Clinical Perspectives on Liver Biopsy and FNA

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Liver Biopsies and Clinical Trials

- Histologic endpoints have had relevance as primary endpoints in nonviral liver disease
  - NAFLD
- For HBV and HCV, virologic or serologic endpoints have been traditional primary endpoint
  - Histologic response as supportive secondary endpoint
  - Intrahepatic analysis generally a research rather than clinical tool
  - For HBV, liver tissue also important (and only reliable) source of cccDNA

The inexorable move to a noninvasive landscape

- Liver biopsies increasingly falling out of favor in clinical practice
- Improving performance of noninvasive fibrosis testing
  - Elastography
  - Serum markers
- With increased attention to functional cure of HBV, how best to assess correlates of immunologically directed anti-HBV therapy?
  - HBV specific T cell responses
- Sampling of PBMC compartment
  - Low yield for HBV-specific T cell responses
  - Fails to reflect critical intrahepatic responses

How to sample the intrahepatic immune environment in a minimally invasive manner?

- While liver biopsies much more accurately capture intrahepatic T cell responses, in general not clinically warranted

- Fine needle aspirations of the liver offer a viable alternative

Fine Needle Aspiration of the Liver

- Historically FNA used to sample focal lesions from a variety of tissues
- Typically yield enriched for mobilizable cell populations
  - Immune cells: lymphocytes, monocytes/macrophages, DCs, NK cells, MAIT cells
- Prior studies have demonstrated that they sample the breadth of immune cell landscape in liver
- Can be done with minimal blood contamination
  - Algorithms to normalize for peripheral blood

Procedural distinctions from liver biopsy

- Size of needle
  - 22-25g vs. 15-16g
- Risk limited compared with percutaneous core biopsy
- Up to 4 passes permissible using introducer needle
- US guidance or blind
- No requirement for sedation
- No absolute need for monitoring
- Can be performed in the office setting

Can FNAs be practically implemented as key exploratory endpoint?

- Need for standardized protocols (aspiration procedure)
- IR suite
- Technician in suite for sample processing
- Minimization of blood contamination (normalization)
- Adequacy of cell yield
- Viability of cells (flash freezing)

FNAs and clinical interventions

- Nuc stop studies
  - Define immune profiles of successful future containment/control
- Immunotherapy
  - Define effects of T cell, innate immune directed therapies on functional responses (e.g., anti-PD1)
  - scRNAseq
- RNAi and other DAAs
  - Assess indirect effect on T cell responses
- Development of biomarkers related to intrahepatic immune profiles

Summary

- FNA capable of reliably sampling the intrahepatic immune environment
- Safe, well tolerated
- Standardizable technique
- Holds promise as exploratory endpoint for HBV treatment trials directed at functional cure