Current Advancements in Liver Replacement: Dialysis, Liver on a Chip, and Tissue Engineering

Natalia D. McIver

BIO 545
Introduction: The Liver

• Functions (over 500 functions)
  – Detoxification
  – Protein Synthesis
  – Heat production
  – Regulation
  – Digestion
Introduction: Complexities of Liver

- Numerous cell types
- Numerous functions
- Highly specific architecture

This is a highly complex organ!
Introduction: The Liver

- Reasons the liver loses functionality
  - Inflammation
  - Liver disease
  - Cancer
  - Hepatocellular carcinoma
  - Autoimmune disorders
  - Drug toxicity
  - Alcoholic and non-alcoholic fatty liver disease

Cirrhosis: a common liver disease
- Affects ~10% of world population and is expected to be #12 cause of death by 2020

www.gmwatch.org
Introduction: The Liver

- Liver failure (acute or chronic)
  - Ultimately liver failure can lead to death
    - Liver disease $\rightarrow$ 1,000,000+ deaths worldwide in 2016
    - Acute liver failure $\rightarrow$ adult mortality $\sim$50%
    - There is a shortage of organs for transplant

The liver is **ESSENTIAL** for our survival
Introduction: Challenges in Liver Regeneration

• Liver has some regenerative capabilities
  – Not enough to repair severe trauma or damage from many diseases

• Complex tissue types
  – Multiple tissue types exist within the liver: this means each tissue would need to be engineered independently

• Complex function
  – Architecture of liver is complex
  – Mechanisms of the different cell types is complex
    • Example: Oxidative function of cytochromes and targeting of toxins is a complex process require highly specific expression
Introduction: The Failing Liver, Options for Care

• When a patient suffers from acute or chronic liver failure, doctors need to find a way to replicate the liver function; they use **Supportive Therapy**

• **Two types of Supportive Therapy:**
  - “Bridge-to-Transplant” (for chronic liver failure):
    • a therapy to help the patient’s liver until they are matched for a transplant
  - “Bridge-to-Recovery” (for acute liver failure):
    • a therapy to help the patient’s liver recover after an injury/illness

**Acute Liver Failure (ALF) algorithm including mortality rate and evaluation for transplant.**
Results: Replacing Liver and/or Liver Function

- **Current Standard of Care**
  - Albumin Dialysis
    - System that removes albumin-bound toxins

- **Research working towards clinical application**
  - Tissue Engineering
    - Growing hepatocytes and supporting cells

- **Research of Bench Top Models**
  - Liver-on-a-Chip
    - Model of a liver that combines tissue, chemical, and mechanical engineering to replicate liver function
Results: Simulating Liver Function

• Albumin Dialysis
  – A system that removes:
    • Albumin-bound toxins
    • Water-soluble substances (ammonia, creatinine, urea)
    • Small proteins (cytokines)
    • Bilirubin, bile acids, glycoside derivatives, phenols, fatty acids
  – Three main types of albumin dialysis:
    • Molecular adsorbent reticulating system (MARS)
    • Single-pass albumin dialysis (SPAD)
    • Prometheus system

Bottom line: Albumin Dialysis separates plasma from blood, removes toxins, and returns “clean plasma” to the body
Results: Comparison of Standard Albumin Dialysis Methods

Figure 1. Extracorporeal nonbiologic liver support albumin dialysis systems. (A) Molecular adsorbent reticulating system (MARS); (B) fractionated plasma separation and adsorption (Prometheus); and (C) single-pass albumin dialysis. Reproduced with permission from Struecker et al.³

Schematic of MARS, Prometheus, and SPAD albumin dialysis methods. Note the subtle differences in dialysis pathways.
Results: Albumin Dialysis Device (MARS)

Example of an albumin dialysis unit.
Results: Bio-artificial Liver Constructs with Tissue Engineering

Criteria for tissue engineering in liver:

- tunable porosity
- Low shear stress
- mechanical stability
- Hemo-compatibility
- High cell-cell interactions
- Cell attachment
  - Berthiaume et. al

Components needed for tissue engineering

Akter, F. Principles of Tissue Engineering
Results: Tissue Engineering with silk Bioscaffold, an example (Janani et al.)

- Which properties of silk make it a viable option for a scaffold?
  - Tunable mechanical strength
  - Biocompatibility
  - Ability to acquire micro molded formats
  - Silk has been used in other tissue regeneration applications, wound healing is one example

- Guided hepatocyte growth has been achieved on porous scaffolds comprised of silk fibroin blended with collagen, chitosan, and galactosylated chitosan

- Silk scaffolds can promote cell attachment and proliferation

- The silk scaffolds created by Janani et al supported cells:
  - The scaffold was able to “maintain long-term hepatic functions for its prospects in bioartificial liver (BAL) development and liver tissue engineering approaches. Cell attachment, proliferation and functional properties of both HepG2 and primary neonatal rat hepatocytes were found to be correlated with the physicochemical properties of the scaffolds.” Janani et al.

Summary: the biocompatible properties of silk were able to support hepatocyte adhesion and proliferation. This is a big deal in tissue engineering!
Surface morphology of freeze-dried silk scaffolds.

Cell Arrangement and Live/Dead Assay

These images allow us to view the scaffold and confirm cellular presence.
**Results: Liver-on-a-Chip**

- **What is it?** A 3-D model that simulates mechanics, functions, and physiological responses of the liver
- **What does it do?** It acts like an artificial organ
- **What's the point of it?** Currently it is used in drug studies and bench top models
- **Can we insert it into my body?** No, there are not any *in vitro* applications at this time
Summary

• The liver is a **necessary** and complex organ
• Albumin Dialysis is not a good long-term solution
  – It is meant to help a patient while they either recover from an acute illness or wait for a transplant
• Progress in tissue engineering is slow:
  – There has been some success in scaffold creation and hepatocyte generation
• Liver on a chip:
  – This technology is currently used for studying pharmaceuticals
  – Chips with up to 4 different functional cells have been successfully fabricated

Reminder: the liver is COMPLEX!

www.elveflow.com
Conclusion

- **Limitations of current technology**
  - Nothing is as efficient as our liver
  - It is difficult to mimic such a complex system

- **Future research is needed**
  - We are not ready for *in vivo* work
  - Understanding cellular interactions and differentiation is important for progress in tissue engineering
  - There is a need for alternative solutions in toxin removal

- **How close (or far) we are to clinical application?**
  - As seen in scientific literature, liver dialysis (bio mimicry technology) is currently in use
  - However, we have a **long** way to go before we can "whip up" a custom liver in a petri dish

**Take home messages:**
- **Advances in tissue engineering are slow**
- **Taking research from bench to bedside is an arduous process**
- **Take care of your liver**
References (page 1 of 2)

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