The National Academies of SCIENCES ENGINEERING MEDICINE

HEALTH AND MEDICINE DIVISION

BOARD ON HEALTH SCIENCES POLICY

Understanding the Role of the Immune System in Improving Tissue Regeneration: Recap of the Day 1 of the Workshop

#RegenMedForum

Keynote address

Ruslan Medzhitov

- Tissue organization is based on structural and functional relationships between different cell types: foundational and supportive cells
- All cells require growth factors and morphogens for their survival and function; mechanisms of local growth factor production are currently not well-understood
- By understanding the circuits that govern cellular interactions in response to different environmental pressures including growth factors, oxygen tension, etc. tissue regeneration should be possible
- Approaches to tissue regeneration should be tailored for specific organ/cell type. Under normal homeostasis, labile cells/organs are repaired by regeneration; stable cells/organs, by regeneration or fibrosis and permanent cells/organs, by fibrosis

Patient perspective

Sherilyn George Clinton

- Have patients needs in mind, because they depend on your research for alleviating their suffering and speeding up their recovery
- We are living at the time of medical ultra-specialization, and it is critical for the scientists to communicate their findings to the public in an accurate and accessible manner

Session I - Immune Tolerance and Graft Acceptance:

Rob Jenq

- There is LOW risk for graft-versus-host disease if the gut is intact with a diverse microbiome OR low bacterial density (decontaminated). There is HIGH risk for GVHD if the microbiome is less diverse or the gut barrier is compromised
- Reverse translation strategies (bedside to bench) especially for dealing with heterogeneous patient populations, provides a fertile ground for generating new hypotheses that can be tested in the lab for improving therapeutic outcomes when translated back to the bedside

Megan Sykes

- Immunosuppressive drugs must be taken for life and have devasting side effects. In contrast, induction of immune tolerance can alleviate many acute and chronic rejection concerns, while leaving the immune system intact
- Most tolerance induction protocols have been shown to work in rodents and not in large animal models or humans. Alternative strategies are needed
- Potentially, cells can be engineered to avoid graft rejection
- Direct differentiation of induced pluripotent stem cells (iPSCs) to hematopoietic stem cells for tolerance induction would be an important advance for the field

Session II- Acceptance of Allogeneic Donor Cells

Sonja Schrepfer

- Transplantation of engineered hypoimmune iPSC- derived differentiated cells may allow avoiding a need for immunosuppression. Some lessons are provided by fetomaternal immune tolerance during pregnancy. Engineering hypoimmune cells (i.e., HLA I and II knockout cells) can promote immune evasion
- Engineered hypoimmune cells: potential safety risks – if these cell do not get recognized/rejected by the immune system, how can we control them?

Katarina Le Blanc

- Local MSC injection is currently more feasible/beneficial than systemic injection. This will hopefully change in the future
- MSC populations significantly differ from each other depending on the tissue of origin. It will be necessary to discover MSC markers that define their biological responses
- It will be necessary to select patients who are more likely to respond to MSC therapies. Currently the data is too complex to predict patients' responses

Bob Valamehr

- Mass production of large batches of fully characterized engineered iPSCs for generation of the off-the-shelf supply of differentiated cells for cell-based therapies is a promising approach
- The iPSCs can be engineered to avoid detection by the host immune system

Session III- Endogenous Regeneration and the Local Environment

Helen Blau

- Prostaglandin E2 (PGE2) augments skeletal muscle regeneration and prevents age-related sarcopenia
- 15-PGDH - the enzyme that degrades PGE2 is a driver of these effects; its level is increased in the aged muscle. Inhibition of 15-PGDH increases PGE2, and is associated with greater muscle mass, strength, and endurance. The NSAIDs inhibit biosynthesis of PGE2 and inhibit muscle regeneration – No Pain, No Gain!

Erika Moore

- Design of biomaterials to study mechanisms of pro-healing and pro-fibrotic responses in vivo
- Recruitment of immature B cells to the site of skeletal muscle injury is associated with pro-healing local responses to injury, and recruitment of mature B cells in associated with pro-fibrotic local responses
- Timing of intervention is a significant factor in strategic modulation of wound healing and regenerative responses

George Hajishengallis

- Del-1, protein is secreted by endothelial cells and macrophages; it promotes inflammation resolution and tissue regeneration in periodontitis and has protective effect against multiple sclerosis and rheumatoid arthritis
- Del-1 expression decreases with aging. Can Del-1 be endogenously activated to counteract the effects of aging?

All

- Combining different modalities for niche manipulation could be a powerful strategy to promote tissue regeneration

Day 2 Reminders

- Welcome back for day 2 of the workshop. We look forward to your participation!
- Ask questions by typing them into the **box below the webcast**
- Please include your name and affiliation with your question
- We will do our best to address as many questions as possible during the panel discussion periods
- Detailed biographies and additional meeting materials can be found in the briefing book

Next Steps

- Keep an eye out for a **survey** in your inbox tomorrow. We would like to hear your thoughts!
- Workshop materials and videos for both days will be posted to the website in a couple of weeks
- A proceedings will be published in 2022 to capture the discussion here

Thank you for participating with

the Forum on Regenerative Medicine!

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