2nd mini symposium series

on Stochasticity and Control in Biological Systems

			ABSTRACT	
29/4/19	11:00	Maya Weinberg	Fruit-bats and their bacteria, in health and in sickness	Tel Aviv University, Sherman buiding. room 330.
	13:00	Imad Shams	Genotoxic stress resistance and cellular senescence in the blind mole rat cells	
15/4/19	11:00	Amiram Ariel	Macrophage engulfment of apoptotic neutrophils controls their decision making during inflammation and its resolution	University of Haifa, Seminar Room at Science compound b
	13:00	Jo Van Ginderachter	Macrophages in the healthy and the tumor-bearing brain: linking single-cell transcriptomics to function	
17/3/2019	11:00	Debora Dunn-Walters	Ageing of the immune system, a BRepertoire Perspective	Bar-Ilan University
	13:00	Yoram Louzoun	Reading the Repertoire	
27/11/2018	11:00	Danny Douek	A Systems Biology Approach to Host Analysis Predicts Susceptibility to HIV Acquisition	Israel Institute for Advanced Studies
	13:00	Michal Horowitz	Environmental stress-Friend or foe. Adaptation and cytoprotive memory vs heat intolerance	
27/5/2018	12:00	Yossi Yovel	From sensory perception to foraging decision making - the bat's point of view	Israel Institute for Advanced Studies
	14:00	Michal Horrowitz	Postponed to 27/11/2018	
22/5/2018	9:30	Josh Milner	Signaling molecules in human immunologic diseases: Basic lessons in immunology and inflammation from rare patients	Weizmann Institute of Science
	11:00	Erez Greenstein (from the lab of Nir Friedman)	TCR repertoires of tumor infiltrating T cells in metastatic breast cancer	
15/5/2018	12:00	Uri Hershberg	History will teach us something - immune system examples of the effects of different scales of selection pressure	University of Haifa
	14:00	Ruth Hershberg	From Boom to bust - the dynamics of bacterial adaptation under prolonged resource limitation From Boom to bust - the dynamics of bacterial adaptation under prolonged resource limitation	

Fruit-bats and their bacteria, in health and in sickness

Maya Weinberg, Department of Zoology, Tel-Aviv University

The host-associated microbiome affects individual health and behavior, and may be influenced by local environmental conditions. However, little is known about microbiomes' temporal dynamics in free-living species compared to those of humans and model organisms, especially in body sites other than the gut. We have investigated longitudinal changes in the fur microbiome of captive and free-living Egyptian fruit bats (*Rousettus aegyptiacus*) a highly common bat all across Israel and neighboring countries, which tends to live in crowded colonies and in high proximity to people in the urban surrounding. We find that in contrast to patterns described in humans and other mammals, the prominent microbiome dynamics are of change over time at the level of the colony as a whole. On average, a pair of fur microbiome samples from different individuals in the same colony collected on the same date is more similar to one another than a pair of samples from the same individual collected at different time points. This pattern suggests that the whole colony may be the appropriate biological unit for understanding some of the roles of the host microbiome in social bats' ecology and evolution. This pattern of synchronized colony changes over time is also reflected in the profile of volatile compounds in the bats' fur, but differs from the more individualized pattern found in the bats' gut microbiome. Less is known about fruit bat's bacterial pathogens that cause morbidity and mortality (unlike viral, fungal etc). In the clinical point of view we encounter persistent seasonal illness throughout the fruit bat colony due to gram positive bacteria. This raises questions about the immunological process evoked in bacterial inflammation of fruit bats and how they cope with bacterial illness. Those questions are yet to be answered.

Research questions -

1. How do bats acquire their own fur and intestinal microbiome? How different events in a bat's life (e.g. meeting conspecifics or visiting new food sources) contribute to the development of this certain microbiome?

2. How do bats transmit bacteria among themselves in a certain colony and among other bat colonies? What is the pace and what is the pattern of this transfer?

3. The bat immune system reaction (innate and acquired) under exposure to bacterial pathogens, in captivity and in nature- How it reflects in physiological and behavioral aspects?

Further Reading-

1. "Coordinated change at the colony level in fruit bat fur microbiomes through time." Nature ecology & evolution 3.1 (2019): 116.

2. "Microbiome analysis reveals the abundance of bacterial pathogens in Rousettus leschenaultii guano." Scientific reports 6 (2016): 36948.

Genotoxic stress resistance and cellular senescence in the blind mole rat cells

Vered Domankevich, Amani Odeh, Irena Manov and **Imad Shams**

The subterranean mole rat, *Spalax*, is a long-lived rodent (~20 years) that tolerates hypoxia and resists cancer, which implies molecular adaptations to prevent genomic instability underlying cancer and aging. We question whether *Spalax* cells resist genotoxic, accumulate less genotoxic lesions, and maintain enhanced repair capacity. Since persistent DNA damage response triggers senescence, we also addressed cellular senescence program in *Spalax* cells. Cellular senescence is an important program evolved to stop the division of damaged cells. Yet such cells also express an inflammatory signature. Accumulating with aging, these cells induce chronic inflammation and support cancer-promoting microenvironment. In this context we investigated whether cellular senescence in *Spalax* cells is associated with inflammatory responses known in human and other animals' cells. In contrast to mouse and human, senescent *Spalax* cells did not accumulate DNA damage and showed undetectable expression of inflammatory cytokines, indicating the uncoupling of the inflammatory response from cellular senescence as a unique feature of *Spalax* senescent cells. Our results strongly support that this species has evolved efficient mechanisms to maintain DNA integrity and to avoid age-related maladies as prerequisites of survival and fitness under the stressful conditions in its subterranean habitat.

Research questions:

- What are mechanisms standing behind the longevity and cancer resistance in this mammalian group?
- What are the driving forces for such uncommon features in rodents?

References:

Resistance to DNA damage and enhanced DNA repair capacity in the hypoxia-tolerant blind mole rat Spalax carmeli. J Exp Biol. 2018 Apr 20;221

Genome maintenance and bioenergetics of the long-lived hypoxia-tolerant and cancer-resistant blind mole rat, Spalax: a cross-species analysis of brain transcriptome. Sci Rep. 2016;6:38624

Pronounced cancer resistance in a subterranean rodent, the blind mole-rat, Spalax: in vivo and in vitro evidence. BMC Biol. 2013.

Macrophage engulfment of apoptotic neutrophils controls their decision making during inflammation and its resolution

Amiram Ariel

**Department of Human Biology, University of Haifa, Israel*

The engulfment of apoptotic leukocytes (efferocytosis) by macrophages during the resolution of inflammation is essential for tissue homeostasis and results in macrophage reprogramming to anti-inflammatory and reparative phenotypes. However, a distinct subset of resolution phase macrophages loss their phagocytic potential, and hence were termed satiated macrophages. Here, we asked whether the loss of phagocytic capacity shapes macrophage phenotype at the molecular and functional levels, and whether novel mediators of resolution can be identified in these cells. We show, using an unbiased RNA-Seq analysis, that satiated macrophages express distinct gene profiles in comparison to phagocytic resolution phase macrophages that can be assigned to differential functions. Particularly, satiated macrophages expressed a distinct IFNβ-related gene signature. Consequently, we determined IFNβ is produced during the resolution of inflammation and facilitated resolution indices, such as PMN apoptosis, macrophage efferocytosis of apoptotic cells and reprogramming to pro-resolving phenotypes. These findings indicate for the first time that IFNβ is a key effector cytokine in resolving inflammation.

Related research questions

Do macrophages govern inflammatory, fibrotic and metabolic disorders through different phenotypes?

Does the loss of phagocytic capacity change the phenotype and function of macrophages during inflammation and its resolution?

Can satiated macrophages serve as a source for resolution promoting mediators?

Suggested reading

New lives given by cell death: macrophage differentiation following their encounter with apoptotic leukocytes during the resolution of inflammation. Ariel, A., and Serhan, C. N. 2012. Frontiers in Immunology, 3:4. doi: 10.3389/ fimmu.2012.00004.

Anti-inflammatory Mechanisms Triggered by Apoptotic Cells during Their Clearance. Szondy, Z., Sarang, Z., Kiss, B., Garabuczi, E., and Köröskényi, K., 2017. Frontiers in Immunology. doi.org/10.3389/fimmu.2017.00909

DELineating resolution of inflammation, Fredman, G., 2019. *Nature Immunology* 20, 2-3.

Macrophages in the healthy and the tumor-bearing brain: linking single-cell transcriptomics to function /Jo Van Ginderachter

Macrophage phenotypes differ between different tissues and even within one tissue. By dissecting border regions of the steady-state brain (choroid plexus, dura mater, subdural meninges) and combining single-cell RNA sequencing with high-dimensional cytometry, bulk RNA-sequencing, fate-mapping and microscopy, we reveal the remarkable diversity of non-parenchymal brain macrophages. Border-associated macrophages (BAMs) residing in these brain regions consisted of distinct subsets that exhibited tissue-specific transcriptional signatures and underwent strong compositional changes during postnatal development. BAM ontogeny correlated with niche accessibility, but subsets displayed distinct self-renewal capacities upon depletion and repopulation.

We then relied on single-cell RNA sequencing to unravel the complexity of the Glioblastoma multiforme (GBM) immune landscape, both in mouse and human. GBM is an invariably fatal primary malignant brain tumor. Within the myeloid compartment, the single-cell data suggest the presence of ontogenically distinct macrophage populations in these tumors, which is corroborated by lineage tracing and adoptive transfer experiments. Multi-parametric flow cytometry allowed for cell sorting of the various macrophage and DC subsets from GBM tumors, which was followed by an extensive functional profiling. This showed clear differences in the macrophage/DC activation state, T-cell stimulatory and suppressive capacities, phagocytic activity and pro-angiogenic potential.

Questions:

1. What would be the fundamentally different functions of tissue-resident versus bone marrow-derived macrophages, if any?
2. Nature or nurture: can ontogenically distinct macrophages become indistinguishable in the same microenvironment?
3. Macrophage depletion or macrophage reprogramming as cancer therapy?

Reading:

- Van Hove H, Martens L, Scheyltjens I, De Vlaminck K, Pombo Antunes AR, De Prijck S, Vandamme N, De Schepper S, Van Isterdael G, Scott CL, Aerts J, Berx G, Boeckxstaens GE, Vandenbroucke RE, Vereecke L, Moechars D, Guilliams M, Van Ginderachter JA*, Saeys Y*, Movahedi K. A single-cell atlas of non-parenchymal brain macrophages reveals ubnique transcriptional identities that are shaped by ontogeny and tissue environment. ***Nature Neuroscience***, in press

- Laoui D, Keirsse J, Morias Y, Van Overmeire E, Geeraerts X, Elkrim Y, Kiss M, Bolli E, Lahmar Q, Sichien D, Serneels J, Scott CL, Boon L, De Baetselier P, Mazzone M, Guilliams M, Van Ginderachter JA. The tumor microenvironment harbors ontogenically distinct dendritic cell populations with opposing effects on tumor immunity. ***Nature Communications.*** 2016. Dec 23;7:13720.

- Movahedi K, **Van Ginderachter J.A.** The ontogeny and microenvironmental regulation of tumor-associated macrophages. ***Antioxid Redox Signal***. 2016 Nov 10;25(14):775-791.

Ageing of the immune system, a BRepertoire® perspective.

Debora Dunn-Walters

Immune repertoire developmental processes are a balance between increasing diversity for maximising shape space and avoiding those shapes that result in autoreactivity. The human immunoglobulin repertoire is a hugely diverse set of sequences that are formed by processes of gene rearrangement, heavy and light chain gene assortment, class switching and somatic hypermutation. Early B cell development produces diverse IgM and IgD B cell receptors on the B cell surface, resulting in a repertoire that can bind many foreign antigens, but which has had self-reactive B cells removed. Later antigen-dependent development processes adjust the antigen affinity of the receptor by somatic hypermutation. The effector mechanism of the antibody is also adjusted, by switching the class of the antibody from IgM to one of seven other classes depending on the required function. There are many places in B cell/immunoglobulin development where positive and negative selection forces can act to shape the immunoglobulin repertoire. In studying normal repertoires in people of different ages we have indications that immune senescence is characterised by a loss of selection, thereby altering the balance between exogenous antigen–specific versus potentially autoantigen-specific sequences. Our studies have also highlighted several questions about the immune system.

Questions

1. How can we use studies of repertoire identify an immunoglobulin that is of importance in vaccine/infection/anti-tumour/autoreactive response.
2. How promiscuous are antibodies and how does this affect the balance between positive/negative selection events?
3. What are the functions of the different classes of antibody in a response and how do they interact with each other in the system?

Reading

Dunn-Walters DK. The ageing human B cell repertoire: A failure of selection? Clin Exp Immunol. 2016 Jan;183(1):50-6. doi: 10.1111/cei.12700. http://onlinelibrary.wiley.com/doi/10.1111/cei.12700/abstract;jsessionid=AB36F0C240017168E6B3698859788D84.f01t03

Laffy JM, Dodev T, Macpherson JA, Townsend C, Lu HC, Dunn-Walters D, Fraternali F. Promiscuous antibodies characterised by their physico-chemical properties: from sequence to structure and back. Prog Biophys Mol Biol. 2016 Sep 14. pii: S0079-6107(16)30047-5. doi: 10.1016/j.pbiomolbio.2016.09.002. http://www.sciencedirect.com/science/article/pii/S0079610716300475

Christian Margreitter, Hui-Chun Lu, Catherine Townsend, Alexander Stewart, Deborah Dunn-Walters and Franca Fraternali, BRepertoire®: A user-friendly webserver for analysing antibody repertoire data http://mabra.biomed.kcl.ac.uk/BRepertoire/ Nucleic Acids Res. 2018 Jul 2;46(W1):W264-W270. doi: 10.1093/nar/gky276.

Reading the repertoire. / Yoram Louzoun

Over the last 10 years advanced tools to sequence B and T cell repertoires were developed. However, we are still lacking methods to read this repertoires in order to understand their relation to the host history and to the development of the immune response.

We present here a few examples of advanced methods to relate the repertoire to the development stages of B and T cells, as well as methods to relate the repetoire to the disease history of the host. These results shed new light on the mechanisms driving selection and development of the repertoire.

and for questions:

What is the optimal representation of B and T cell sequences to infer their relations with antigens?

How much of the repertoire is random and how much is actually related to some response.

What are the main check points in repertoire development.

Reading:

Evidence for shaping of light chain repertoire by structural selection. A Toledano, Y Elhanati, JIC Benichou, AM Walczak, T Mora, Y Louzoun. Frontiers in immunology

Converging evolution leads to near maximal junction diversity through parallel mechanisms in B and T cell receptors

JIC Benichou, JWJ van Heijst, J Glanville, Y Louzoun. Physical biology 14 (4), 045003