BITS :: Call for Abstracts 2022 - Oral communication

Type	Oral communication
Session	Multi-omics / bio-medical knowledge management
Title	Not all fetal gonadal macrophages are alike: a tale of three phenotypes
All Authors	Valentina Lorenzi (1, 2), Cecilia Icoresi Mazzeo (2), Luz Garcia-Alonso, (2), Roser Vento-Tormo (2)

Affiliation

(1) EMBL-EBI, Cambridge, UK
(2) Wellcome Sanger Institute, Cambridge, UK

Motivation

Gonadal development is a complex process that involves sex determination followed by divergent maturation into either testes or ovaries. Tissue-resident immune cells are thought to play an important role in gonadal development and function, with testicular macrophages having recently gained momentum for their putative role in male fertility. In this study, we set out to investigate the immune composition of the human fetal gonads using single-cell transcriptomics (scRNA-seq) and multiplexed single-molecule fluorescence in situ hybridisation (smFISH).

Methods

We profiled human gonadal and adjacent extragonadal tissue from the first and second trimester of gestation (6 to 21 post-conceptional weeks, PCWs), covering stages of sex determination and differentiation into ovaries and testes (female n=33; male n=22). For each sequenced scRNA-seq library, we performed read alignment to the GRCh38 reference genome, quantification and quality control using Cell Ranger. We used Scrublet for cell doublet calling on a per-library basis. We used a two-step diffusion doublet identification followed by Bonferroni-FDR correction and a significance threshold of 0.01. We integrated the filtered count matrices from Cell Ranger and analysed them with the Scanpy pipeline following their recommended standard practises. A variational autoencoder-based method (scVI) was employed to reduce the dimensionality of the data specifying the donor as a batch.

To study the unique profile of our gonadal macrophages, we downloaded and analysed myeloid datasets from multiple developing tissues: liver, skin, kidney, yolk sac, gut, thymus, placenta, bone marrow and brain. We then merged them with our gonadal myeloid cells using scVI with a combined batch of donor and sample to integrate across the different organs. We also projected osteoclasts and microglia from these datasets onto our gonadal immune manifold using a Support Vector Machine (SVM) model.

Results

Our analysis showed that most gonadal immune cells in the first and second trimester of gestation are macrophages with a tissue-repair phenotype (LYVE1, F13A1, FOLR2), previously defined in other developing organs. Unique to the developing testes, we find two rare macrophage populations which we validated with smFISH: (i) SIGLEC15+ fetal testicular macrophages (ftM), with an osteoclast-like signature (SIGLEC15, ACP5, ATP6V0D2), and (ii) TREM2+ ftM, with a microglia-like signature (TREM2, P2RY12, SALL1). Integration and projection with an SVM of scRNA-seq datasets of myeloid cells in other developing organs onto our gonadal immune manifold validated the shared transcriptomics profile between SIGLEC15+ ftM and osteoclasts, and between TREM2+ ftM and microglia.

smFISH imaging revealed a specific and distinct localisation of the two ftM populations in the fetal testes. SIGLEC15+ ftM distribute in the interstitial space close to endothelial cells. SIGLEC15+ ftM also express COL1A2 - which can potentially interact with the integrins expressed by endothelial and mesenchymal cells - as well as the matrix remodelling molecule MMP9. On the other hand, TREM2+ ftM are often found inside the testicular cords, where we predict they communicate with Sertoli and germ cells via the interaction between TREM2 and apolipoproteins. TREM2+ ftM also have their phagocytosis machinery active.

These results suggest a synergistic role of the two ftM populations in overseeing testis development: TREM2+ ftM in removing damaged or apoptotic cells while minimising inflammation and oxidative stress that could damage maturing germ cells; SIGLEC15+ ftM in promoting mesonephric endothelial cell migration, a transient process required for testicular cords formation (~8-14 PCWs). More broadly, we envision macrophages with a microglia-like profile to be likely involved in seeding immunoregulatory microenvironments, while macrophages with an osteoclast-like phenotype to enable extracellular matrix remodelling needed in neovascularization processes.

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Corresponding Author	
Name, Surname	Valentina, Lorenzi
Email	vlorenzi@ebi.ac.uk
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Società Italiana di Bioinformatica
C.F. / P.IVA 97319460586
E-mail bits@bioinformatics.it

Sede legale Viale G. Mazzini, 114/B - 00195 Roma
Website bioinformatics.it