Computational analysis of gene expression datasets to unravel the basis of graft versus host disease

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October 28, 2015

Graft versus host disease

- In malignant pathologies the donor immune system recognises tumour cells as foreign and eradicates them via immunological mechanisms which together are known as the graft vs tumour (GVT) effect
- Donor immune cells may also attack normal host tissue resulting in acute graft vs host disease (GVHD)
- The skin, liver and gastrointestinal tract are the most common tissues to be damaged in GVHD
- GVHD remains one of the most common post-transplant complications and represents a major barrier to the successful application of allo-HSCT
- A major risk factor involved in GVHD pathology is the use of HLA-mismatched, non related donors
- Acute GVHD involves alloreactive donor T-cell mediated cytotoxic response to the tissues of the recipient
- Tissue damage caused by cytotoxic T cells leads to recruitment of other effector cells including natural killer cells which further increases tissue injury and results in self perpetuating GVHD
- Mice represents the primary model animal for pre-clinical studies of GVHD
- Mouse models of acute GVHD usually involve a bone marrow transplant (BMT) which is supplemented with varying numbers/types of donor lymphocites into irradiated allogenic recipients who differ from donors in their MHC class 1 and/or class 2 molecules or in minor histocompatibility antigens

The ImmGene project

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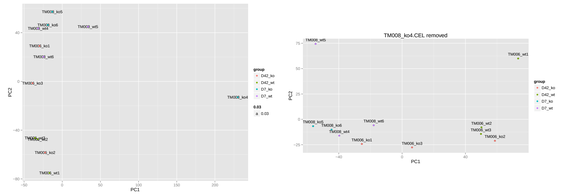
T-cell expression in multiple minor histocompatibility antigen-mismatched BMT model

Objective: In a polyclonal model, evaluate the differences in gene expression of effector T cells found in the lymphoid organs or in the peripheral tissues.



- PCA analysis of all samples reveals presence of outlier in the D7 dataset (***TM*008$_k$*o4***)
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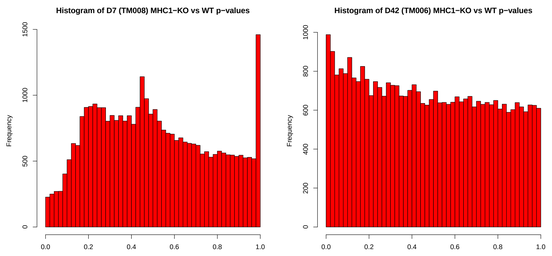

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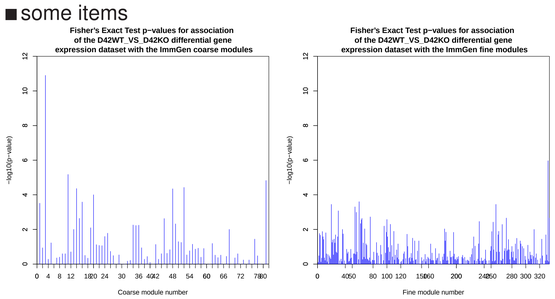
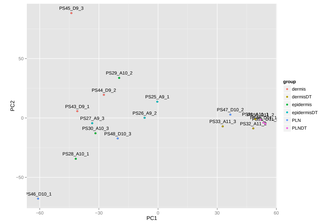


gene name	fold change	pvalue
Ptbp2	0.8575669378	0.0002380649
Trappc1	-0.8105321657	0.0011522667
Mrpl32	-0.9482075354	0.0015174569
Ctso	0.6665616898	0.0015502065
Cib1	-0.5435813927	0.0022304297
Chordc1	-1.1641319443	0.0033252187
Actr6	-0.7619741241	0.0034636625
Pcgf5	-0.6144202783	0.0035618031
Llph	-0.797961394	0.0047160713
1810037I17Rik	-0.6327137658	0.0053622021
Cd46	1.2478436705	0.0077584292
Zfp455	-1.3221395229	0.0083646381

T-cell expression: Single minor histocompatibility antigen-mismatched BMT model

Objective: In a monoclonal model, evaluate the effect of depleting Langerhans cells on the gene expression of effector T cells found in the lymph nodes and in the skin.



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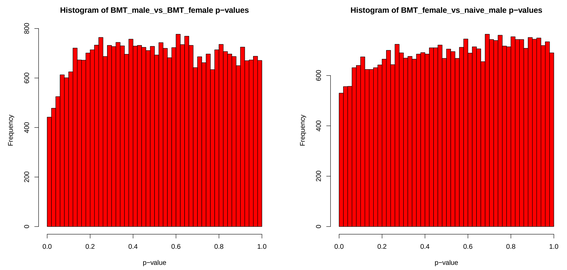

- Histogram of BMT male vs naive male p-values appears to show a more consistent distribution with the null hypothesis
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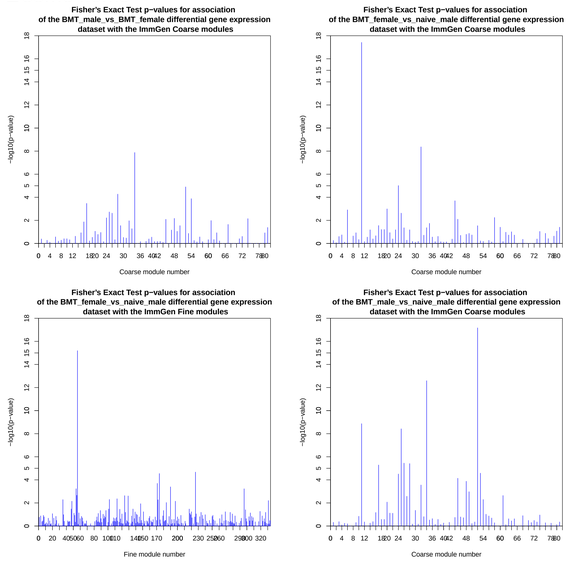
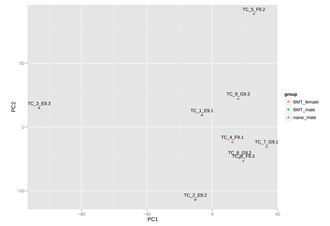


Langerhans cell expression

Objective: Evaluate the differences in gene expression of Langerhans cells in the setting of an allogeneic BMT or a syngeneic BMT.



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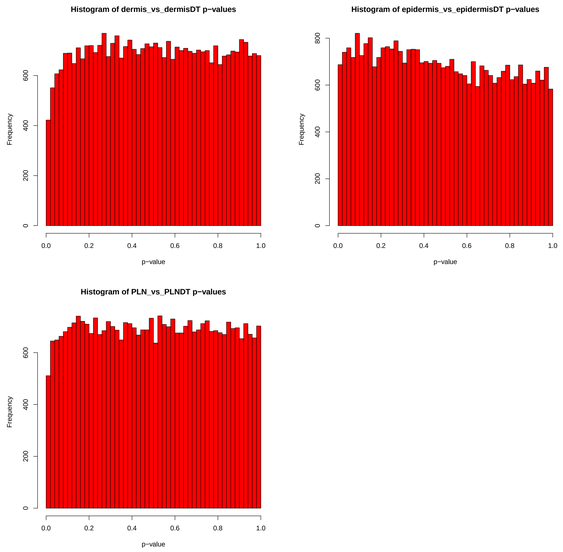

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