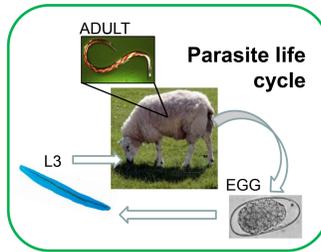


Identifying and exploiting the molecular basis of resistance to gastrointestinal parasites in sheep

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1. The Parasites

New **control alternatives** are required for the management of *Teladorsagia circumcincta*, a **common** species of nematode parasite that infects sheep in the UK, due to the presence of widespread (**multiple**) **drug resistant** parasites in sheep flocks.



2. The Alternative

Sheep **acquire resistant immunity** with exposure to parasites. Sheep vary in resistance, which is a **heritable** trait. This makes **breeding for resistance** possible.

3. Sheep Immune System

T helper cells are believed to be crucial to the development of resistance or susceptibility. Naïve T helper cells can mature into 1 of 3 subsets once activated by parasite proteins in the gut.

➤ T helper type 2 (**Th2**) cells produce a protective response in the sheep gut and contribute to **antibody production** and **parasite expulsion**.

➤ **Th1** and **Th17** cells exacerbate pathology causing **inflammation** in the gut and persistence of the parasites.

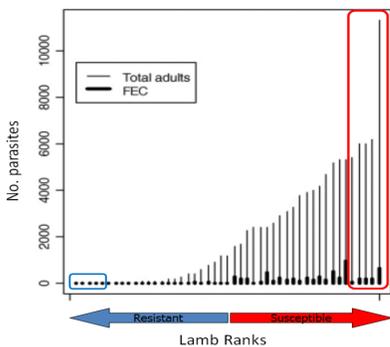


- Aims:**
- 1) Understand how sheep respond to nematode infection
 - 2) Understand and identify the genes associated with the response
 - 3) Identify variation within those genes which may contribute to resistance
 - 4) Identify genetic markers for selective breeding of livestock



1. Understanding response to infection

Methods:



47 parasite-naïve 12 week old female Blackface lambs were persistently artificially infected with *T. circumcincta* larvae for 13 weeks.

Abomasal lymph node tissue from 5 infected lambs that completely cleared the infection (**'RESISTANT'**), 5 infected lambs that did not clear the burden (**'SUSCEPTIBLE'**) and from 5 uninfected **'CONTROL'** lambs was used for Affymetrix microarray analysis validated by quantitative-PCR cytokine array. Significantly differentially expressed genes were analysed by Ingenuity Pathway Analysis to identify gene networks and functions.

Results:

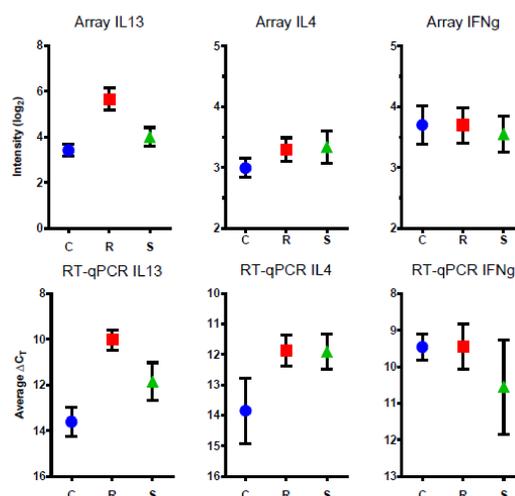
Top networks identified by Ingenuity Pathway Analysis

Resistant vs. Control	Score
Humoral Immune Response, Protein Synthesis, Inflammatory Response	48
Haematological System Development and Function, Haematopoiesis, Tissue Morphology	28
Cardiovascular System Development and Function, Cellular Movement, Gene Expression	22
Hereditary Disorder, Skeletal and Muscular Disorders, Tissue Morphology	21
Cell Signalling, Molecular Transport, Vitamin and Mineral Metabolism	20

Susceptible vs. Control	Score
Cell-To-Cell Signalling and Interaction, Haematological System Development and Function, Immune Cell Trafficking	24

Resistant vs. Susceptible	Score
Antigen Presentation, Lipid Metabolism, Small Molecule Biochemistry	18

Most differentially expressed cytokines in Affymetrix and qPCR array



Conclusions

- These results confirmed our hypothesis, and corroborate previous work, that the **Th2** response pathway is crucial for the development of **resistance**.
- Whilst, the **Th1/Th17** response pathway is activated in **susceptible** animals.

Further work

- **Sequence** and **identify variants** within the transcription factors controlling differential T cell activation and **quantify** their expression levels in these experimental animals.
- **Genotype** for variants in the Exlana flocks maintained by Sheep Improved Genetics Ltd.

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Original study performed by: JM Pemberton, D Beraldi, BH Craig, J Hopkins. 2011. *Molecular Ecology* 20:910-919

Results above published by: A Gossner, H Wilkie, A Joshi and J Hopkins. 2013. *Veterinary Research* 44:68