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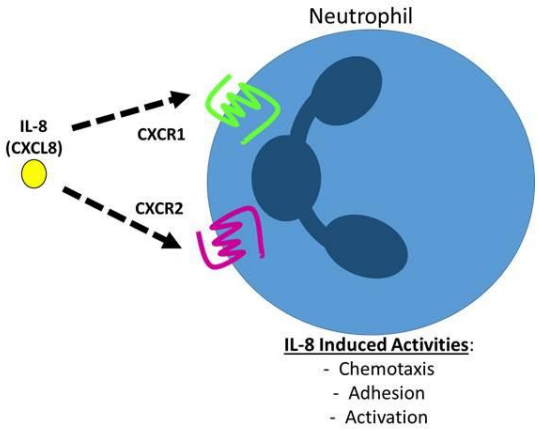
Interleukin 8 haplotypes and disease susceptibility in cattle



Key external stakeholders:

SFI, DAFM, Teagasc commercial partners, dairy industry

Practical implications for stakeholders:

- Interleukin 8 is a protein which 'calls in' neutrophils during infection.
- We have discovered two versions of the gene which makes this protein in cattle and have now validated that calves carrying each version have a different immune response profile.
- We have also shown that 50% of Holstein-Friesian cattle are carrying the alternative gene, whereas 100% of Jersey cattle are.
- We determined that genetic variation in this gene is associated with somatic cell score (SCS), thereby identifying cows with reduced SCS.

Main results:

- Cells from version (haplotype 2) cattle are more responsive *in vitro*, and produce higher levels of the IL8 protein that version 1 cattle.
- Calves carrying each version of the IL8 gene have distinct immune response profiles when stimulated with the bacterial endotoxin (LPS) *in vivo*.
- This version of the gene is also associated with elevated somatic cell score in >5700 Holstein-Friesian dairy cows.

Opportunity / Benefit:

Genetic variation uncovered during this project has been added to the IDB SNP chip to identify the relationship between this gene and other traits of agricultural interest, including health and longevity traits. A follow on project is assessing the role of this gene in protecting against viral infection.

Collaborating Institutions:

TCD

Contact Kieran Meade Email: Kieran.meade@teagasc.ie.

Teagasc project team: Dr Kieran Meade (PI)
External collaborators: Professor Rachel McLoughlin, Trinity College Dublin

1. Project background:

Significant variation exists in the responses of individual cattle to infection. This variation contributes to enhanced protection on one hand, while contributing to inflammation and pathology on the other. Identification of genes associated with protective immunity would facilitate the selection of cattle with superior health traits. We have uncovered two distinct and highly polymorphic versions of a gene in the Holstein-Friesian population that were hypothesized to have relevance to the immune response in calves as well as cows.

2. Questions addressed by the project:

- What frequencies do these versions exist at in other cattle populations?
- Do these versions confer different immune responses using bovine cells *in vitro*?
- Can these results be validated *in vivo*?
- Do these genetic variants contribute to differences in cell function?
- Do these genetic variants contribute to differences in Somatic Cell Score?

3. The experimental studies:

A number of molecular biological assays were performed in cells of bovine origin *in vitro* to identify if genetic variants conferred differences in immune response. A panel of calves representing both IL8 haplotypes were purchased, subjected to an experimental challenge with bacterial endotoxin (under licence) and their immune response was profiled. Finally a genome-wide association study was performed between IL8 haplotype and Somatic Cell Score.

4. Main results:

- Cells from version (haplotype 2) cattle are more responsive in vitro, and produce higher levels of the IL8 protein that version 1 cattle.
- Calves carrying each version of the IL8 gene have distinct immune response profiles when stimulated with the bacterial endotoxin (LPS) *in vivo*.
- This version of the gene is also associated with elevated somatic cell score in >5700 Holstein-Friesian dairy cows.
- Genetic variation at the IL8 locus therefore explains a proportion of the inter-breed and inter-individual variation in immunity between neonatal calves which is likely to influence their resistance to infection.

5. Opportunity/Benefit:

Genetic variation at the IL8 locus therefore explains a proportion of the inter-breed and inter-individual variation in immunity between neonatal calves which is likely to influence their resistance to infection. It also contributes to the mechanisms regulating Somatic Cell Score. This finding will contribute to on-going efforts to breed for disease resistance.

6. Dissemination:

Main publications:

Stojkovic, B., Mullen, M.P., Donofrio, G., McLoughlin, R.M. and Meade, K.G. (2017) 'Interleukin 8 haplotypes drive divergent responses in uterine endometrial cells and are associated with somatic cell score in Holstein-Friesian cattle' *Vet. Immunol. Immunopathol*. Feb;184:18-28. doi: 10.1016/j.vetimm.2016.12.006. Epub 2016 Dec 16. PMID: 28166928.

Stojkovic, B., McLoughlin, R.M. and Meade, K.G. (2016) '*In vivo* relevance of polymorphic Interleukin 8 promoter haplotype for the systemic immune response to LPS in Holstein-Friesian calves' *Vet. Immunol. Immunopathol.* Dec;182:1-10. doi: 10.1016/j.vetimm.2016.09.006. Epub 2016 Sep 18. PMID: 27863538.

Contact Kieran Meade Email: Kieran.meade@teagasc.ie.

Presentations:

Research was presented at multiple national and international conferences including:

1. Agricultural Research Forum, Tullamore Ireland, March 2015.
2. The Association for Veterinary Teaching and Research Work, 47th Annual Scientific Meeting, Hillsborough, Co. Down, Northern Ireland, UK – October 2013.
3. 10th International Immunology Symposium, University of Milan, Italy - September 2013.
4. BSAS Annual Meeting, University of Nottingham, UK – April 2013.
5. The Association for Veterinary Teaching and Research Work, 48th Annual Scientific Meeting, Backweston, Cellbridge, Ireland – October 2014.
6. 4th European Veterinary Immunology Workshop, The Royal College of Physicians, Edinburgh, UK – September 2012.

Popular publications:

- Stojkovic, B., Meade, K.G., McLoughlin, R. (2014) 'Genetics and disease resistance' *Tresearch*, 9 (1).

7. Compiled by: Dr Kieran Meade

Contact Kieran Meade Email: Kieran.meade@teagasc.ie.