



EDITORIAL

Genetic resistance to infectious diseases: A complementary tool to antimicrobial drugs in livestock?

La resistencia genética a las enfermedades infecciosas: ¿una herramienta complementaria a las drogas antimicrobianas en la producción pecuaria?

A high percentage of the world's population depends on livestock for their sustenance. Therefore, animal health is closely linked to food safety and security, as it is essential to ensure that the food consumed is safe and not contaminated with pesticides, residues and microorganisms that pose a risk to public health. Traditionally, the control and eradication of infectious diseases on domestic animals have relied on the use of antibiotics and vaccines. Furthermore, sub-therapeutic doses of antimicrobials have been widely used as growth promoters in animal production. This overuse and misuse of antimicrobials in veterinary medicine has raised public concern and drawn attention to the livestock industry (including mammals, poultry and aquaculture) due to the development of antimicrobial-resistant zoonotic organisms and the presence of antimicrobial residues in animal products intended for human consumption⁴.

In this century, the European Union has either banned the use of antimicrobials in animal production or implemented barriers that hinder their use. Similarly, within the framework of the "One Health" concept, which involves various interdisciplinary sectors to address the risks that arise at the interface of human, animal and environmental health, Argentina passed Law No. 27233 in 2015, declaring animal and plant health, as well as the prevention, control and eradication of diseases and pests affecting national forestry, agricultural production, flora, and fauna, to be matters of national interest.

Given this reality and the enormous need to maintain animal protein production, a new area of research has emerged, focusing on alternatives to replace or reduce the use of antimicrobial drugs. Thus, phytochemical feed additives, pre-, pro- and postbiotics, enzymes and other natural compounds have gained attention as antimicrobial alternatives used in the livestock industry¹. These compounds have potential to improve animal health and performance,

restore gut microbial balance, eliminate harmful pathogens, boost immunity and promote nutrient absorption.

At the same time, the study of natural resistance to infectious diseases in livestock has emerged as a complementary tool in the fight against microorganisms. Natural resistance is defined as the innate ability of an organism to defend itself against infectious diseases or to develop milder clinical symptoms than others when exposed to a specific pathogen, without prior vaccination. Innate resistance to infectious diseases has been known since the early 19th century, after repeated observations over time that clinical manifestations of infectious disease rarely occur in all members of the population exposed to the same pathogen under similar conditions. Genetic variability plays a key role in host responses to parasitic, bacterial, fungal and viral infections, influencing both disease establishment and progression. It is widely accepted that variability in susceptibility to bacterial infections, within and among ruminant breeds, is partially determined by host genetics; however, estimated heritability is generally low to moderate ($0.1 < h^2 < 0.2$). The mechanisms underlying these observations were initially unknown until the development of molecular biology tools and, later, the arrival of the "omics" era, when the association of natural resistance to pathogens with genetic markers across animal species, breeds or families could be established. The genetic regulation of natural resistance to infectious diseases is variable and often complex and includes both immune and non-immune mechanisms.

Case-control genetic association studies (AS) evaluate whether a genotype variant occurs more frequently in individuals displaying a specific phenotype compared to those who do not, resulting in an estimated correlation between polymorphisms, disease outcomes or associated traits (i.e., serologically positive vs. negative animals in flocks highly exposed to the specific pathogen). While genome-wide (GW)

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AS analyze thousands of single nucleotide polymorphisms (SNPs) across the genome, enabling to identify new genomic regions putatively related to disease susceptibility, candidate gene (CG)-AS are *a priori* hypothesis-driven analyses that limit the study to one or a few polymorphisms, resulting in an increased statistical power to detect genetic associations. Several CG- and GWAS were reported for tuberculosis, paratuberculosis and mastitis in cows showing significant associations of natural resistance with polymorphisms within, for example, *SLC6A6*, *FKBP5*, *PTPRT*, *NOS2*, *TNF*, *KARLN*, *MyD88*, *MAP3K1*, *BMPR1B* and *BoLA-DRB3* genes⁵. Moreover, a more limited number of CGAS were reported for bovine brucellosis and bacterial infections in small ruminants that mainly studied polymorphisms in genes encoding for cytokines, toll-like receptors (TLRs), natural resistance-associated macrophage protein 1 (NRAMP1), and genomic regions previously identified by GWAS for another host or pathogen³. Similarly, several studies found genetic variation among individuals and breeds of chickens, pigs and fish, resulting in different genomic expressions that confer resistance against major avian, swine and fish pathogens. Genetic variants involved in disease resistance and susceptibility in these animal species were observed in genes encoding the major histocompatibility (MHC) molecules (associated with antigen presentation, antibody production, and cytokine stimulation), TLRs, immunoglobulins, cytokines, interleukins, B cells and CD4+ and CD8+ T-lymphocytes.

Unfortunately, putative associated variants have often demonstrated very little effect on disease susceptibility in field trials; and to date, subsequent association studies and experimental assays for validation and functional characterization of the associated variant are often unsuccessful or never performed. This limitation arises partly because genetically controlled resistance to infectious diseases is a polygenic trait, and many disease problems are not caused by single pathogens but rather, they are syndromes caused by multiple pathogens, exacerbated by stress or nutritional challenges and influenced by local microbiota and physiological conditions. Despite the aforementioned limitation, association studies are very useful to identify genetic determinants of complex diseases. Gene function is commonly elucidated using genetically modified rodents; however, the role of genes during disease progression is usually studied by linking genetic variations to disease phenotypes in a clinical setting.

Even though the genetic basis and mechanisms involved in differential resistance to infectious diseases remain largely unknown, natural resistance to infectious diseases appears to be a very promising tool for controlling infectious diseases in livestock. The generation of livestock genome sequences and other tools and resources that enable

large-scale studies of, for example, epigenetics, alternative splicing, microRNAs and transcription profile, will greatly enhance the ability to select for increased disease resistance through genetic markers and gain a deeper understanding of the biological basis of host resistance and the pathways involved in the response to pathogens. Soon, advanced technologies, such as the CRISPR-Cas9 system, will facilitate cost-effective host genome editing and the development of resistant breeds, which would significantly reduce antibiotics use in livestock. Selection for resistance to specific diseases could lead to undesirable consequences on susceptibility to other diseases, and simultaneous selection for a high ability to mount both antibody- and cell-mediated immune responses, represents a major challenge. Likewise, researchers should be wary of whether a lower incidence of diseases would be genetically correlated with reduced production traits², as future breeding strategies should aim to improve or at least maintain health and fitness.

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