EPIGENETIC IN LIVESTOCK ANIMALS: A NEW PERSPECTIVE FOR HOST-PARASITE RELATIONSHIP AND A POSSIBLE TOOL FOR A SUSTAINABLE PARASITE CONTROL

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Dear Editor,

Livestock animals have been selected for docility and functionality for the last 10 thousand years and up until the middle of last century, phenotypic traits were used to improve these characters. One of the most important traits is the complex relation of the animals' resilience to parasite infection. The diagnostic of helminth infections still relies on laboratory (parasite egg count) and clinical (anemia, apathy, weight loss) examinations, contributing to the decision for parasite control (FERREIRA et al., 2018). Modern tools of biotechnology and genetics have allowed us to explore some of the animals' natural characteristics (PCR, sequencing) and determined and map gene/protein function (qPCR, Western blot, 3D electrophorese).

The over use of chemical treatments, has led a number of parasites to develop resistance to the products, in a fast population selection process. As an increase consequence, we have seen a growing global concern around parasite resistance in the last forty years in livestock animals. New drugs have been studied (i.e. derquantel, monepantel), as well as other management options, such as selective treatment, the use of phytotherapy, and the genetic selection of the host have gained importance (MOLENTO, 2009). However, the research on parasite control have been ignoring a huge field of the biological area, the epigenetics.

Although the origin of the epigenetic term came to light in the 40's with Conrad Waddington, describing the epigenetic landscape, this science field became notorious only in the past two decades. Epigenetic studies accounts for the biological events that could not be explained by genetic principles. As a definition, epigenetics describes the causal interactions between genes and their products, which bring the phenotype into being (WADDINGTON, 1942). Epigenetics is also known as the link between genotype and phenotype, without changing the DNA sequence.

The search for the term "epigenetic" on SCOPUS (www.scopus.com) database returned almost 90.000 documents, as more than 70.000 were published in the last 10 years. The medical area of oncology was the highest epigenetic area in progress. Just to make an unfair comparison, when we looked for the keywords "cancer AND epigenetic" it returned almost 30.000 results, whereas the search for "parasite AND epigenetic" returned only 560 articles. If we look closely at these searches, we found that the vast majority of the studies regarding parasites focused parasites of human importance (eg. toxoplasmosis, lice) (n=496), while those restricted to veterinary were clearly minimal (n=65). This is just a small evidence of how parasitology, and even more veterinary parasitology, is belated regarding epigenetic potential discoveries.

The epigenetic defines the idea in which the environment play an important role in gene regulation, through the so-called epigenetic modifications or events. A fundamental feature of these events is that they can regulate gene expression without changing the DNA nucleotide sequence. The three main epigenetic events are DNA methylation, histone post translational modifications and non-coding RNAs. All these modifications rely on an intricated pathway with many potential targets for disease monitoring and treatment.

Another notable feature of the epigenetic events is its heritability. Exposure to environmental stressor can provoke epigenetic changes in male or female germ cells. These changes are inherited by its offspring and can lead to a transgenerational heritability (DEWALS et al., 2019). Initial clinical studies have reported the first data that maternal parasite, from helminth infections, may influence the immune profile in their offspring and this factor can continue for the offspring's entire life. Thus, we hypothesize that when this knowledge is transposed to veterinary parasitology in the future, an epigenetic based biomarker can be used for the identification of individuals that are susceptible or resistant/resilient to parasite infections. Moreover, host selection programs could largely focus on epigenetic markers, keeping tolerant animals in the herd/flock to reduce livestock losses, to improve farm resilience and to significantly reduce the number of anthelmintic usages, improving sustainability.

Although it may sound far away from the clinical practice, many biomarkers and drugs (called "epidrugs") targeting an epigenetic modification are already approved and in use for diseases, such as cancer and some neurological disorders. For example, the methylation profile of *GTPS1* gene is currently used in clinical practice for the diagnose of prostate cancer in humans. Also, drugs that inhibit DNA methylation, such as azacitidine and decitabine, are already approved and are in use for the treatment of many hematological malignances in human (BERDASCO; ESTELLER, 2019). Epigenetic based biomarkers and epidrugs for other diseases such as neurological, metabolic, immunological and virus diseases are already in pre-clinical or in clinical trial phase. Regarding parasitic disease, we can find studies on parasite of veterinary and human relevance such as *Plasmodium*, *Toxoplasma* and *Schistosoma*, but it lacks research on parasites that are exclusive to animals. In short, epigenetic is a reality in human medicine practice, but it is not for veterinary medicine.

Therefore, we think that epigenetic is an expanding field of study and it has an underexplored potential to study the host-parasite relationship and parasite control protocols. These benefits would be applied through the development of “epidrugs” as the new generation therapy directed to key parasites. It would also be possible to establish heritable biomarkers for resistant/resilient animal selection to reduce the use of chemicals (i.e. less environmental contamination), prolonging their lifespan and the parasite resistance process.

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