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

EPIGENÉTICA EM ANIMAIS DE PRODUÇÃO: UMA NOVA PERSPECTIVA NA RELAÇÃO PARASITO-HOSPEDEIRO E UMA POSSÍVEL FERRAMENTA PARA O CONTROLE SUSTENTÁVEL DE PARASITOS

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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, specific phenotypic traits were used to improve these characters, focusing more on milk and meat production and prolificity. Although largely neglected, 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 exams, such as parasite fecal egg count and on-farm clinical examination of anemia, apathy, and weight loss – to name a few. After obtaining these information, the field veterinarian would then decide for the most proper parasite control strategy (FERREIRA et al., 2018). Lately, more modern tools of biotechnology, including proteomics, and functional genetics have allowed us to explore some of the animals' genetic characteristics (MA et al., 2020), using PCR, and sequencing and also determine and map gene/protein functions based on qPCR, Western blot, and 3D electrophorese. Even though these tools are not readily available to most of the laboratories, the research area is expanding very fast.

A common practice of parasite control is the recommendation of antiparasiticides to animals. But the over use of chemical treatments, has led a number of parasites to develop resistance to these products, in a fast population selection process – even to the most recent anthelmintic compounds. 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, which focus the treatment to the most infected animals, the use of phytotherapy or their principal components, and the genetic selection of the host have gained importance (MOLENTO, 2009). However, the research on veterinary 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. Thus, 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 (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,

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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 possible heritability, meaning positive and negative. Exposure to environmental stressor can provoke epigenetic changes in male and female germ cells of parents and some of these changes can be inherited by its offspring, leading to a transgenerational heritability (DEWALS et al., 2019). Lacal & Ventura (2018), have recently divided these epigenetic changes in three types: the direct epigenetic form (changes during the lifespan), and the indirect ones, the within (inside the womb, during gestation) and the across (family lines: grandparents, etc.) processes. The epigenetic evidences looking for the across type is considered the faster route of information. Initial clinical studies have reported the first data that maternal parasite infections from helminths, 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 individual animals 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, improving farm resilience. The animal identification based on epigenetic processes could significantly reduce the number of anthelmintic uses and the parasite resistance process, prolonging their lifespan. When heritable biomarkers are identified it would also be possible to improve environmental sustainability by lowering the use of pour-on or spray acaricides to control ticks (*Rhipicephalus microplus*) and horn-flies (*Haematobia irritans*).

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 azacytidine 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 diseases, we found studies on zoonotic parasites 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 and research, but it is not for the veterinary medicine. It clear that epigenetic is an expanding field of study and it has an underexplored potential to better elucidate the host-parasite relationship and be applied into more sustainable parasite control programs. These benefits would be applied through the development of "epidrugs" as the new generation therapy directed to key parasites of livestock.

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