Livestock Breeding for Disease Resistance: A Perspective Review

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Livestock Breeding for Disease Resistance: A Perspective Review

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ABSTRACT

Livestock plays a momentous role in a country's economy especially in a developing nation like India, where livelihoods of about 20.5 million people depend upon livestock and its allied sectors, suggesting that about two-third of the rural community is involved (Annual Report, 2018). The small ruminants like sheep and goat provide main source of income for many economically poor people, especially marginal and landless farmers. Similarly the role of these livestock to various pastoral communities cannot be ignored. So whenever there is a disease outbreak, the burden of huge economic loss falls on these poor livestock keepers. The traditional methods of disease management involve either treatment with antibiotics or vaccination for prevention of diseases. However, the indiscriminate use of these antibiotics has lead to antibiotic-resistant pathogens and likewise it is extremely difficult to develop vaccines against a wide range of pathogens that are frequently mutating and are caused by multi etiological factors. Hence, considering all these factors breeding of disease resistant animals becomes a top priority in this changing world. The literature is filled with references of indigenous animals and poultry being resistant to many diseases. Keeping this in view, the current review has been written to highlight sustainable and feasible methods for breeding them for disease resistance.

Key words: Breeding, Disease, Indigenous, Livestock, Resistance.

The theory of disease resistance is a complex and dynamic process of host parasite or host pathogen relationship. The term commonly refers to individual's fight to infection *i.e.*, a host's ability to moderate the pathogen and also resistance to consequences of the contagion. The defence mechanism against the pathogens or parasites by living hosts can be divided into two broad classes: resistance and tolerance. The resistance mechanisms actively reduce the pathogen burden, whereas tolerance mechanisms limit the impact of disease caused at any particular burden (Roy and Kirchner 2000, Miller *et al.* 2005). It is well known that in a disease outbreak only the resistant animals survive. So when restocking of livestock population is done after the calamity, the main objective of a breeder would be to select only the resistant animals that can survive with minimum input and managemental practices. Therefore, the first consideration will be disease tolerance, *i.e.,* within a population, some individuals are more tolerant to specific pathogens. Secondly, there is resilience, which determines whether an individual can recover from illness. Both tolerance and resilience are dependent on host and pathogen genetics and they complicate the path from infection back to health (Richardson, 2016). So, a very important precondition for developing disease-resistant animal varieties will be to understand the variability mechanisms of the important pathogen(s) and identifying evolutionary dynamics of various defence systems of host–pathogen interactions.

Understanding immunogenetics

The study of genetic basis of the immune response is known as immunogenetics. The term was introduced with the discovery of ABO blood groups and were first demonstrated through the existence of "natural" antibodies *i.e.*, isoantibodies (Landsteiner, 1901). The broad field of

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immunogenetics include study of normal immunological pathways as well as identification of genetic variations that result in immune defects, which may facilitate detection of new therapeutic targets for immune diseases. Hence, understanding and subsequent manipulation of host immune response (immunomodulation) is the most precise and effective tool to reduce disease incidences and nullify the limitations associated with antibiotic treatment or vaccination. Therefore, breeding for disease resistance has gained considerable attention from researchers in the recent past.

Immune response genes

Often it was observed that individuals respond differently to same infectious agent. A possible explanation may be the

genetic variability between them. Indeed, many studies have looked for associations between genes involved in immunity and disease outcome (Buniello *et al.* 2019) and it has been found that certain immune response (*Ir*) genes play the crucial role.This concept was discovered in the mid-1960s (McDevitt and Benacerraf, 1969) and this discovery introduced an apparently new level of antigen recognition whose diversity and specificity had to be explained in addition to those of familiar immunoglobulins. Hence immune response (*Ir*) genes were defined as antigen-specific genes that control the ability of an animal to raise an immune response, either humoral or cellular to a particular antigen (Berzofsky, 1980). This includes Major Histocompatibility Complex (*MHC I, II* and *III*), Interleukins (*IL−6, IL-β*), Tumor necrosis factor (*TNF-α*), cluster of differentiation (*CD-14*) and Toll like Receptor (*TLR-4*), which are responsible for conferring innate immunity. They code for set of cytokine or anti inflammatory response complement proteins (C1-C4) that adhere to pathogens and cytokines (interferons and chemokines) that attract immune cells to the site of infection. The MHC gene complex appears to play a central role in all immune functions and disease resistance. All the higher animals possess a MHC gene complex that codes for the predominant cell surface proteins on the cells and tissues of each individual of the species (Snell *et al.* 1976). The MHC encodes three classes of protein molecules-class I, class II and class III (Matzinger and Zamoyska. 1982). The first class of molecules consist of a membrane-bound glycoprotein heavy chain with a molecular weight of 40,000 to 50,000 and a non-membrane bound light chain, 32-microglobulin, molecular weight of 12,000. The class II molecules are membrane-bound glycoproteins consisting of two non-covalently associated chains, α and β, each with a molecular weight of about 30,000. Class III molecules are components of serum complement. From a study by Kannaki *et al.* 2017 it was highlighted that LEI0258 microsatellite based MHC typing would be a useful tool in sorting cross-bred and indigenous chicken populations, selecting birds for breeding programs. In another study Kannaki *et al.* 2018 attempted to explore TLR gene family, TLR gene expressions in day-old duckling tissues by real-time PCR and also investigated the cytokine expression in peripheral blood mononuclear cells (PBMCs) upon TLR agonist's stimulation in *in vitro* assay. It was found that TLR gene expression in young ducklings together with cytokine response upon LPS stimulation demonstrated the innate preparedness of younger birds to encounter pathogens and their functional ability to respond to their ligands. The relative expression of interleukins (IL)-1β, IL-2, IL-6, IL-17 and interferon (IFN)-Y genes were explored in response to coccidial challenge in Kadaknath, Cari-Vishal and Cobb broiler chicken using quantitative PCR (Thakur *et al.* 2020) and it was concluded that the differential expression of cytokine genes in the three genetic groups showed different degree of mucosal immune response to *Eimeria* infection and it depended upon the genetic

background or genotype of birds, coccidial dosage and age of infection. Some of the *Ir* genes and their association with disease resistance in livestock and poultry are given in Table 1.

Main challenges for selection towards disease resistance

The biggest challenge is identifying the phenotype for disease resistance. If animals are solely selected based on health status which may lead to selecting animals having subclinical infection and they may become carriers or reservoirs for the infectious agent. Thus the selection for a disease resistant trait is limited, as it becomes difficult to identify and measure the traits. Selection for resistance to particular pathogen may result in indirect selection for a more virulent pathogen. Thus, maintenance of the host's immune defence system in homeostasis may be complicated. However, in certain situations breeding for disease resistance can be a viable option like when therapeutics or vaccination is not effective *e.g.* in case ofavian influenza or African swine fever. The virus is highly mutagenic due to frequent antigenic shift as well as drift. The stamping out of the stock causes great economic loss and involves grave ethical concerns. Therefore, the development of a disease-resistant stock is a good alternative.It may also be effective in case of diseases with multi etiological agents. For example mastitis is an economically important disease of dairy animals, caused by many pathogens ranging from gram-positive to gram negative bacteria. It may also play a significant role in developing antibiotic free products leading to organic production, without the use of any drug, therapeutics or vaccination.

Broad strategies of breeding for disease resistance

Selection of healthy animals based on natural infection

In this approach, only healthy animals, without any sign or symptom for the disease will be selected randomly. However, the accuracy of selection decreases if animals are not arbitrarily subjected or exposed to pathogen. The greatest advantage of this method is that it is easier to employ, involves less cost and does not possess any ethical concern. This has been employed in selection of Red Maasai sheep in Kenya, which were observed to be more resistant than South African Dorper breed to *Haemonchus* infection (Mugambi *et al.* 1996).

Selection of animals after artificial infection

Here, attempts are made to improve the accuracy of selection by uniformly challenging animals under study with infections of similar doses of the infective agent. This methodology is more precise by having random distributions of pathogen among the animals under study. However, the main constraint is that the process is costly depending upon the pathogen's virulence and clinical expression of disease and possesses ethical concerns. This may require isolation of the population to prevent transmission to other stock. For example, challenge study has been used for selection of

Table 1: Some examples of immune response genes in livestock and poultry with their references.

Species	Example	Reference
Cattle and Buffalo	The MHC of cattle, known as the bovine leukocyte antigen (BoLA) complex, plays an integral role in disease and parasite susceptibility and immune responsiveness of host.	Fries *et al.*1986
	Higher hemolytic complement activity in *Bos indicus* breeds is associated with higher resistance to tick infestation as compared to *Bos taurus* breeds.	Wambura *et al.* 1998
	The *Nramp*1 (natural resistance-associated macrophage protein) gene has been linked with resistance to brucellosis, tuberculosis and salmonellosis.	Adams *et al.* 1999
	The association of bovine leukocyte antigen major histocompatibility complex class II DRB3*4401 allele with host resistance to *Amblyomma americanum* tick.	Untalan *et al.* 2007
	The relationship between Bovine Lymphocyte Antigen DRB3.2 alleles, somatic cell count and milk traits in Iranian Holstein population suggesting higher susceptibility to subclinical mastitis.	Pashmi *et al. 2009*
	A region on chromosome 1 was associated with infectious keratoconjunctivitis (pinkeye) in cattle, which is heritable.	Kizilkaya *et al.* 2013
Sheep and Goat	The Visna-Maedi Virus (VMV) infection increases expression level of MHC Class II in lung, CNS and synovium.	Singh *et al.* 2006
	Genetic resistance to *Haemonchus contortus* infection block initial colonization of larvae and have an efficacious Th2 type response.	Bishop and Morris, 2007
	Functional analysis of significant differentially expressed genes, such as *SLC9A3R2, FCER1G, GSK3A* and *FCER2*, revealed a crucial association with cellular homeostasis maintenance and immune response.	Yang *et al.* 2015
	The genetic diversity of Sirohi goat for DQB and DQB1 loci was studied and their association with antibody response induced by the Peste des petitsruminants vaccine was recorded.	Gowane *et al.* 2018
Pig	Single genes influencing disease resistance, including the fimbriae *F4* (K88) gene for reducing *E. coli* intestinal infection, have been identified. The use of receptor-free boars might be beneficial in herds with diarrhoea problems.	Gibbons *et al.* 1977
	Porcine MYD88 is a key protein in the TLRs/IL-1R signalling pathway that sends inflammatory signals and enhances intensity of inflammatory response.	Sun *et al.* 2015
Poultry	Single-strand conformational polymorphisms and sequence polymorphisms have linked MHC I and MHC II to resistance against salmonella.	Liu *et al.* 2002
	Resistance to Salmonella has also been linked to different genes like ILs, IFNγ, TLRs, iNOS and genes involved in apoptosis. Resistant chicken lines showed a higher expression of interleukins like IL-2, IL-6, IL-8 and IFNγ in the small intestines as compared to susceptible chicken lines.	Rebel *et al.* 2005
	Studies on Beijing-You chicken have revealed 39 SNPs associated with different immunological traits against avian influenza virus.	Zhang *et al.* 2015
	MHC plays a vital role in resistance against Marek's Disease.	Smith *et al.* 2016

disease resistance in sheep against Strongyle infection (Terefe *et al.* 2007). The immune responses to *Haemonchus contortus* infection were compared in studies in resistant Barbados Black Belly (BBB) and susceptible INRA 401 (INRA) breeds of lambs. A more persistent and elevated Th2 cytokine mRNA transcription and blood eosinophilia were noted in BBB lambs, during primary and secondary artificial challenges.

Artificial infection of relatives or clones of animals

This strategy is aimed to challenge relatives or clones of the breeding stock. This is very useful in disease having very high mortality rate. Ideally, it should be done in highly controlled and isolated environment. This is probably not practical, but publicly funded institutions may develop such testing facilities in the future. However, one limitation of the above methods is biasness, as they do not consider the immunological background of the animals under study. Robert *et al.* 2005 were successful in creating transgenic cattle that express a bacterial protein lysostaphin in their milk in order to increase their resistance to mastitis induced by *Staphylococcus aureus*.

Indirect selection

It can be doneeither by selection of indicators for disease resistance *i.e.*, pathogen reproductive rates, somatic cell

count or immunological response of the host, such as Faecal Egg Count.For effective selection, indicator traits must be heritable, highly genetically correlated with resistance to disease or diseases of interest, accurate to measure and affordable (Snowder, 2006). The genotype environment interaction also plays a significant role in the process of selection. Thus, selection programs have to be environment-specific, with the selection environment matching the commercial production environment. One of the most successful approaches of indirect selection for disease resistance has been reported in sheep by selecting for low faecal internal parasite egg count (Woolaston *et al.* 1992). In dairy cattle, somatic cell count has been used as selection criteria for reducing mastitis incidence (Shook and Schutz, 1994).

Marker-assisted or genomic selection

Marker-assisted selection (MAS) for disease resistance involves identification of markers aided through polymorphism for the immune-response genes or identification of single-nucleotide polymorphisms (SNPs). The SNPs for certain immune-response genes have been reported for the *CD14* gene in goat and cattle (Pal and Chatterjee, 2009; Pal *et al.* 2011 respectively). An advantage of MAS is that information is available at avery early age of life which saves the huge cost of rearing animals to their age of production. Considering the polygenic nature of inheritance, the better approach to MAS is genomic selection. The SNPs for the genes involved in disease resistance are identified, preferably with SNP chips and GWASs can be done with suitable software.

Advanced strategies

However, some of the advanced strategies for breeding for disease resistance have been developed to edit the genes at molecular level. In the year 2006 andrew Fire and Craig C. Mello shared the Nobel Prize in Physiology or Medicine for their work on RNA interference (RNAi) in *Caenorhabditis elegans* (Fire *et al.* 1998). In this biological process RNA molecules inhibit gene expression, typically by causing the destruction of specific mRNA. This pathway is conserved in most eukaryotic organisms and have evolved as a form of innate immunity against viruses. Since its discovery and regulatory potential, it has become evident that RNAi has immense potential in the suppression of target genes. Likewise, Emmanuelle Charpentier and Jennifer Doudna have been given the 2020 Nobel Prize in Chemistry for their discovery and development of CRISPR-Cas9 (clustered regularly interspaced short palindromic repeat/Cas9) genome editing (Jinek *et al.* 2012). It was derived from the CRISPRs found in bacteria that serve to identify or destroy foreign DNA. The RNA-guided endonucleases utilized a short guide RNA to recognize DNA, bind an endonuclease and induce site specific cleavages. This cutting edge tool has contributed towards many important discoveries in basic research and clinical trials of new disease therapies. Very recently it was utilized to cut out a small section of cluster of differentiation 163 (*CD163*) gene in pig DNA that interacts

with the porcine reproductive and respiratory syndrome (PRRS) virus and this modification prevented the virus from causing any infection (Burkard *et al.* 2017). Similarly, CRISPR-Cas9 mediated targeting of the ASFV p30 gene was also done to convey resistance against African Swine Fever infection (Hübner *et al.* 2018).

CONCLUSION

Thus, it is well known now that breeding for disease resistance utilises proven animal breeding methods and other molecular tools to improve animal health and productivity. Naturally, it is receiving more and more attention from livestock breeders and becoming more common throughout the world. The list extends from nematode resistant sheep in Australia and New Zealand (Stear *et al.* 1997) to mastitis resistant cattle in Scandivia (Heringstad *et al.* 2000) or selection of pigs with high immune response which shows increased response to commercial vaccines and increased growth rate (Wilkie and Mallard, 2000). Simultaneously, the poultry producers have long been aware of the use of breeding to improve resistance to avian lymphoid leucosis complex and Marek's disease (Cole, 1968). However, there are two concerns about the desirability of breeding for disease resistance (Stear *et al.* 2001). The first is that there may be unfavourable consequences for other diseases or production traits and second concern is that many diseases are rare or episodic. In conclusion, it isalso observed that heritability for traits related to disease resistance indicate that selective breeding is feasible. Therefore, further investigation is necessary to define any adverse associations between disease and production traits. Hence, breeding for enhanced disease resistance is a readily available method to improve animal welfare and productivity in a variety of situations.

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