

## Editorial

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# Heat Stress and Gut Health in Broilers: Role of Tight Junction Proteins

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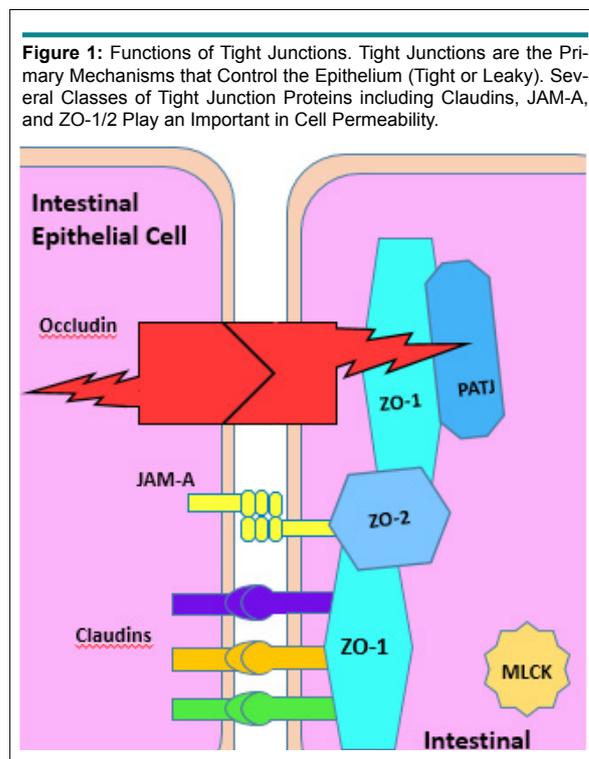
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## INTRODUCTION

Sixteen of the seventeen hottest years ever recorded have occurred since 2001 and climate trends are predicted to continue in an upward trend.<sup>1</sup> As this upward trend continues, it will serve as a severe environmental stress factor on all forms of the life.<sup>2,3</sup> One of the most affected industries will be the livestock industry. Poultry, in particular, appears to be very heat sensitive animals, due to lack of sweat glands and high metabolic activity.<sup>4,5</sup> It is estimated that heat stress alone costs the U.S. poultry industry more than 100 million dollars a year and this number is expected to rise.<sup>6</sup> For broiler (meat-type) chickens, the external temperature for optimal performance is 18 to 22 °C.<sup>7</sup> Under these conditions, the internal body temperature of a broiler is between 40.6 °C-41.7 °C. Nevertheless, when chickens are placed under heat stress conditions, their body temperature may be well above that; up to 45 °C-47.2 °C, which is the lethal limit.<sup>8</sup> Heat stress (HS) or hyperthermia results from failed thermoregulation that occurs when animals produce or absorbs more temperature than it dissipates.<sup>9</sup> The adverse effects of HS can range from discomfort to multiple organ damage and, under severe stress, to death by spiraling hyperthermia. The Gut plays a vital role in nutrient absorption, digestion and transport, yet it is very responsive and susceptible to HS. In this editorial we will review the effect of heat stress on tight junction (TJ) proteins and gut health.

## HEAT STRESS AND GUT HEALTH

Under thermoneutral conditions, the gut is able to efficiently digest and absorb most nutrients through cell plasma membranes (transcellular transport) that involves specific receptors. Epithelial cells in the intestine provides a barrier isolating the external environment from the internal body, yet, providing tolerance to water and digested nutrients.<sup>10-12</sup> Intestinal epithelial cells adhere to each other through three distinct intercellular junctional complex known as desmosomes, adheren junctions (AJ), and TJ (Figure 1). Desmosomes are localized dense plaques that are connected to keratin filaments while AJ and TJ both consist of transcellular proteins.<sup>13,14</sup> These proteins are connected intracellularly through adaptor proteins to the actin cytoskeleton.<sup>3,15</sup> In contrast to transcellular transport, the transfer of molecules through the space between the cells across an epithelium (paracellular transport) is passive down a concentration gradient, and this transport is regulated by the TJ.<sup>16</sup> As multi-protein complexes, TJ not only hold cells together, but they form channels allowing the transport of substances across the epithelium.<sup>17</sup> Interestingly, the molecular composition, ultrastructure, and function of TJ is regulated by intracellular proteins through a series of intracellular signaling pathways that includes myosin light kinase (MLCK), mitogen-activated protein kinases (MAPK), protein kinase C (PKC) among others.<sup>18</sup> Occludin phosphorylation on Tyr, Ser and Thr is associated with disruption of TJ, hence, phosphorylation of occludin is involved in TJ permeability.<sup>19</sup> Any factors that affect the balance between protein kinases and protein phosphatases, such as heat stress or inflammation can affect gut permeability due to disruption of TJ.<sup>20,21</sup> In contrast, glycosylation of the Junctional adhesion molecule-A (JAM-A) decreases gut permeability.<sup>22,23</sup> TJ regulate epithelial permeability and paracellular diffusion *via* two pathways, leak and pore.<sup>24</sup> The leak pathway allows transport of large noncharged solutes while the pore pathway allows the transfer of large charged molecules.<sup>25</sup> As transmembrane barrier proteins, TJ also function as a fence between the lumen and host.<sup>26</sup> There are roughly 50 TJ proteins, which include the



claudins, occludin, tricellulin, JAM's, and scaffolding proteins. For instance, tricellulin (also known as MARVELD2) and angulin family proteins, including angulin-1 (also known as LSR), angulin-2 (also known as ILDR1) and angulin-3 (also known as ILDR2), have been identified as molecular constituents of tricellular contacts. Both types of proteins are involved in TJ formation as well as the full barrier function of epithelial cellular sheets. The primary role of scaffolding proteins is to regulate stand formation and placement of transmembrane proteins.<sup>4,27</sup> Under thermal neutral conditions, paracellular junction are rigorously regulated.<sup>14</sup> However, under heat stress conditions, the TJ barrier becomes compromised and luminal substances leak into the blood stream, hence the term leaky gut,<sup>28</sup> a condition that induce chronic systemic inflammation which requires high resources of energy that impact negatively the performance of the animals. Alterations in gut permeability are associated with bacterial translocation (BT) in the portal and/or systemic circulation in several types of leaky gut syndromes leading to systemic bacterial infections.<sup>29</sup> Similarly, FITC-dextrin is a large molecule (3-5 kDa) which does not usually leak through the intact gastrointestinal tract barrier.<sup>4,6</sup> However, when there are conditions which disrupt the tight junctions between epithelial cells, the molecule can enter circulation demonstrated by an increase in trans-mucosal permeability associated with chemically induced disruption of tight junctions by elevated serum levels of FITC-d after oral administration.<sup>30,31</sup> Although studies are very limited, it has been reported that cyclic heat stress up regulated claudin and ZO-1 expression in the chicken jejunum.<sup>32</sup> This indicates that heat stress dysregulates intestinal barrier function and induces leaky gut *via* alteration of tight junction proteins which merit further in depth investigations.

#### CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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