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Role of immunohistochemistry for diagnosis of non-infectious diseases

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Abstract
Immunohistochemistry (IHC) is utilized to understand the distribution and localization of biomarkers and separately expressed proteins in various parts of animal tissues such as ovary, uterus. It can assist in differentiating muscular dystrophy from non-dystrophic disorders in muscle diseases. Diagnosis of cancers is done with the help of IHC because specific tumor antigens are expressed *de novo* or up-regulated in certain cancers. IHC plays an important role in diagnostic dermatopathology, marker selection and interpretation is highly informed in clinical context and the histologic differential diagnosis. Recently, the applications of novel IHC markers in melanoma diagnosis containing genetic mutation status markers e.g. BRAF (v-raf murine sarcoma viral oncogene homolog B) and NRAS (neuroblastoma RAS viral oncogene homolog) and an epigenetic alteration marker is highlighted (e.g. 5 hydroxymethylcytosine).The IHC findings of the normal canine skin both cytokeratin 8 (ck8) and ck18 expressions were detected in the glandular epithelium of apocrine sweat glands, but not in myoepithelial cells. No immuunoreactivity for ck8 and 18 was seen in sebaceous, hepatoid glands and in all epidermal layers. Bone Morphogenetic Protein (BMP) is found in the cytoplasm of tumor cells of osteosarcoma and chondrosarcoma. BMP-McAb detects the BMP and inhibits the generation of new bone. This also makes it potentially useful in diagnosing, treating, and providing a prognosis for osteosarcoma and other bone diseases. Immunoreactivity SPY (synaptophysin) was observed predominantly in the tunica muscularis and myenteric plexuses. While, a less immunoreactivity was found in the lamina propria, submucosa and serosa in goat (Garcia *et al.*, 2014). NNE (non-neuronal enolase) -positive neuroendocrine cells were identified at a later stage than SPY (synaptophysin) -positive cells. The staining distribution and intensity patterns for the two factors were similar except that NNE (non-neuronal enolase) staining was prominent in the epithelium of all forestomach compartments in sheep and deer. In the IHC staining technique, a strong positive reaction for cytoplasmic IgG bearing B- lymphocytes was detected within the germinal centers of lymphoid nodules, towards the base of the follicle-associated epithelium (FAE) and some cells even infiltrated the crypt epithelium. In the mantle zone and internodular area, reaction was very mild showing that T- lymphocytes predominated in these areas. Lung alveolar macrophages were negative for CD34 and Willebrand factor (vWF) but were positive for CD31 with a membranous pattern of staining. The nuclei of endothelial cell (EC) of the different vessel types in the lungs were diffusely stained by friend leukemia virus induced erythroleukemia (Fli-1) in human. However, the nuclei of lymphocytes were also stained, as well as the cytoplasm of some alveolar wall cells probably corresponding to mastocytes. The cardiomyocyte's structure is compromised and there is a disorganization of desmin filaments and loss of cross striation in the course of heart failure. In dog kidneys, epithelial tubular cells lose their cytokeratin staining characteristics and transdifferentiate into cells exhibiting a key mesenchymal feature of vimentin-positive staining in glomerulonephritis. In human histiocytic disorders, the tumors that originated from macrophage lineage exhibited high expression of lysozyme, whereas those arose from dendrite cell had low expression or devoid of this molecule. Immunohistochemically, calbindin-D9k (CaBP-9k) and vitamin D receptor (VDR) immunoreactions were limited to the endometrial epithelia of all examined animals. But, both repeat breeder buffalo-cows and anestrus showed remarkable lower uterine expressions for CaBP-9k and VDR in comparison with normal cyclic ones.

Keywords: immunohistochemistry, non-infectious diseases, animals

Introduction
Immunohistochemistry (IHC) has become a tool widely used for diagnosis in human pathology since the 70's. But its application in veterinary diagnostic pathology has not been so common, especially because of the lack of specific antibodies. In basic research, IHC has become an important technique and is widely used in many medical research laboratories. IHC is utilized to understand the distribution and localization of biomarkers and separately expressed proteins in various parts of human and animal tissues such as ovary (Abd-Elkarim, 2017) [1] and uterus (Abd-Elkarim, 2017) [1].

IHC is used in the field of mesenchymal stem cells (Yang *et al.*, 2010) [129], embryonic stem cell (Fenderson *et al*., 2006 [48]; Nethercott *et al.,* 2011 [98]) and Telocytes (Qi *et al*., 2012) [104] research. Since, IHC can detect the earliest changes in transformed tissues and identify cellular changes which are not normally visible with Hematoxylin and eosin, it can be used to distinguish hyperplasia from neoplasia (Okoye *et al*., 2015) [100]. It is used in the histopathology of the respiratory system and routine diagnosis of lung cancer (Linnoila *et al*., 1984; Capelozzi, 2009; Leite *et al*., 2010) [89, 21, 87], differential diagnosis and classification of soft-tissue tumors (Muro-Cacho, 1998; Hornick, 2014) [96, 72], diagnosis of prostate cancer (Betta *et al.,* 2012) [16], surgical pathology practice (Jambhekar *et al.,* 2008) [76], in the Diagnosis of Bioterrorism Agents (Guarner *et al*., 2006) [66], in mammary pathology and breast cancer (Yeh, 2008) [131], diagnosis of cutaneous Leishmaniasis (Dias *et al.,* 2017) [41] and in oral pathology laboratory (Ajura *et al.,* 2007) [6]. IHC is helpful to establish timing of a traumatic injury in medico-legal settings (Duraiyan *et al*., 2012) [43]. It can also assist in differentiating vascular dystrophy from non-dystrophic disorders in muscle diseases (Duraiyan *et al.,* 2012) [43]. immunohistochemistry is being used with increasing frequency to identify underlying molecular changes or the presence of specific molecular markers in tumors, both as an aid to diagnosis and as a guide to appropriate therapy (Chauhan *et al*., 1998 [28]; Joshi and Chauhan, 2012 [77]; Singh and Chauhan, 2018 [116]). There are three major classes of genogenic immunohistochemistry: (a) identification of specific mutations, by documentation of loss of expression of the corresponding protein, as exemplified by E-cadherin in lobular breast cancer; (b) identification of proteins expressed as a consequence of specific translocations, such as the t(2;5) translocation of anaplastic large cell lymphoma leading to ALK protein expression; and (c) identification of molecular targets of novel tumor therapies (Genogenic IHC will help to identify underlying molecular changes that can be used both for diagnosis and therapy, Gown, 2002). Usage of automated computerized image capture and analysis systems (Cregger *et al.,* 2006 [38]; Jambhekar *et al.,* 2008 [76]) will give more accurate results. Development of more specific antibodies from recombinant antibody fragments gives molecules with ultra-high affinity, high stability, and increased potency (Jambhekar *et al*., 2008) [76]. Tissue Microarrays [TMA] as a high-throughput method which enables the economical evaluation in terms of sample utilization and reagent costs (Cregger *et al.,* 2006 [38]; Jambhekar *et al.,* 2008 [76]). IHC is a significant application of monoclonal as well as polyclonal antibodies to find out the distribution of tissue of an antigen of interest in health and disease (Chauhan *et al*., 2001 [27]; Chauhan and Chandra, 2007 [24]; Chauhan and Rana, 2010 [25]). Diagnosis of cancers is done with the help of IHC because the specific tumor antigens are expressed *de novo* or up-regulated in certain cancers. IHC plays a significant role in pathology, especially in the subspecialties like oncologic pathology, neuropathology, and hematopathology (Kumar *et al*., 2002 [85]; Singh and Chauhan, 2018 [116]; Harit and Chauhan, 2020 [68]). Immunohistochemical stains the intermediate filaments that are expressed by tumor cells (keratin, desmin, vimentin, neurofilaments, and glial fibrillary acidic proteins) (Yang *et al.,* 2011) [130]. Use of specific antibodies against microbial DNA or RNA is done to test the infectious agent in tissues through IHC techniques (Chauhan, 1995 [29]; 1998 [28]; 2010 [25]). IHC staining for beta amyloid precursor protein is helpful in detecting axonal injury within as little as 2–3 h of head injury (Nethercott *et al.,* 2011) [98]. Specific diagnosis of muscular dystrophy is essential because of the genetic counseling hints of inherited disease and accurate prognostication (Chauhan and Tripathi, 2002) [26]. In muscular dystrophies, abnormalities in several muscle proteins have been identified recently. Such abnormalities involve proteins located in the extracellular matrix, sarcolemma, cytosol, nucleus and other sites within muscle fibers (Fenderson *et al.*, 2006) [48]. Skeletal muscle biopsy can play an important role in differentiating vascular dystrophy from non-dystrophic disorders. IHC stains were used distinguish malignant lymphoma and anaplastic carcinoma and in the identification of amelanotic melanoma (Chauhan, 2003) [30]. IHC stains help in diagnostic decision making when evaluating many lymph node biopsies or extra nodal hematopoietic/lymphoid infiltrates, particularly if flow cytometric studies have not been performed (Banga *et al*., 2008) [13]. The myoepithelial cells expressed a strong immunostaining for -SMA, Ck14 and Cx43 biomarkers. Bovine and caprine mammary glands revealed that the spatial distribution of myoepithelial cells is variable in the different segments of the alveolar–ductal system in IHC studies. Deshmukh *et al.,* (2010) [40] observed unique tumorous cell response to Ki-67 was moderately to highly reactive, a nuclear proliferation marker, while noticeable response to cytoplasmic cytokeratin 7 (CK7) and low to poor reactivity towards cytokeratin 20 (CK20) in atypical transitional epithelium and invasive cell nest. They observed exhibition of various grades of adipose tissue (AT) alterations, CD68 positive cells that were localized in AT from 10 early lactating Holstein cows. Adipose tissue biopsies from over-conditioned, non-pregnant, non-lactating cows were analyzed for CD68 positive cells by using IHC technique (Häussler *et al*., 2017) [69].

Skin

IHC can acts as an important adjunct in the diagnosis of neoplastic skin diseases. In addition to the various established IHC markers currently in use, new markers continue to emerge, though their general acceptance and routine application requires robust validation. Recent applications of novel IHC markers in melanoma diagnosis containing genetic mutation status markers e.g. BRAF (v-raf murine sarcoma viral oncogene homolog B) and NRAS (neuroblastoma RAS viral oncogene homolog) and an epigenetic alteration marker is well highlighted (e.g. 5 hydroxy methyl cytosine).The role of IHC in the differential diagnosis of cutaneous lesions which is categorized into melanoma, spindle cell lesions of the dermis, epidermal tumors with an intraepidermal epitheliomatous pattern, small round blue cell tumors of the dermis, and cutaneous adnexal tumors is also well known. IHC plays an important role in diagnostic dermatopathology, marker selection and interpretation which is highly informative in clinical context and the histologic differential diagnosis (Compton *et al.,* 2015) [35]. Skin has internal positive controls for the majority of antigens which is used as markers of neoplastic lesions, including melanocytes, keratinocytes, Langerhans cells and Merkel cells, as well as vessels, muscle and nerve bundles (Lian and Murphy, 2014) [88]. For example, the cells of secretory coils of eccrine sweat glands are positive for low-molecular-weight cytokeratin as well as CK7, epithelial membrane antigen (EMA), cell adhesion molecule 5.2 (CAM 5.2) and carcinoembryonic antigen (CEA), but acrosyringeal cells of the intraepidermal

portion of sweat glands are positive for high-molecular-weight cytokeratins (HMWCK). A critical first step in the interpretation of IHC staining is careful observation to positive and negative internal controls (Compton *et al.*, 2015) [35]. Haemangiosarcomas mainly reported in the dog and cat and are less common in the cow, horse, pig and goat, but no cases in sheep. In internal sites, these tumors are occurring more commonly in the subcutis. The normal or the neoplastic endothelial cells do not react with the antibodies anti-Factor VIII-related antigen (FVIII-RAg) and anti-CD31, whereas at various stages of differentiation, the normal and the neoplastic cells labelled endothelin-1 strongly reacts. The results heighten the use of endothelin-1 as a vascular marker in sheep in the IHC detection of neoplastic endothelial cells. IHC assays were conducted using commercially accessible antibodies to the pan T-lymphocyte marker CD3 and B cell antigen receptor complex CD79 alpha (Sapierzyński, 2010) [111]. Immunohistochemically, the specific marker for mast cells are used as CD117 antibody or c-KIT and it helps in the diagnosis of less differentiated Mast Cell Tumors (MCTs) in canine (Reguera *et al.*, 2000) [109]. Three KIT-staining patterns are presented which are membrane-associated staining (KIT I), focal-to-stippled cytoplasmic staining with decreased membrane-associated staining (KIT II), and diffuse cytoplasmic staining, (KIT III) (Kiupel *et al.*, 2004) [84]. Apparently, tumours with the most atypical expression (cytoplasmic staining/ KIT II or KIT III) have a poor prognosis (Kiupel *et al.*, 2004 [84], Webster *et al.*, 2006 [125]). The immunophenotypic markers of Langerhans cells contain MHC-I, MHC-II, CD1a, CD1c, CD11b, CD11c, CD18, CD44, CD45, CD45RA, CD49d, ICAM-1 and E-cadherin (Ginn *et al.*, 2007, Baines *et al.*, 2008, Ramos-Vara & Miller, 2011) [60, 12, 106]. But these antibodies are not available to the Veterinary researchers and most of these antibodies are utilized in fresh or frozen tissue. Only the CD45, CD45RA, CD18 and E-cadherin antibodies are used in formalin-fixed, paraffin-embedded tissues (Affolter & Moore 2002 [5], Fulmer & Mauldin, 2007 [55], Gross *et al.*, 2008 [65]). VIM (vimentin) immunostaining was restricted mainly to the dermis, while melanosome was restricted to the epidermal stratum basalis and root sheath of the hair follicles (El-Shafey *et al.*, 2017) [45]. The present study revealed localization of VIM in the fibroblasts and endothelia of the blood vessels, similar to that recorded in the skin of the American buffalo and pig (Cho *et al.*, 2006; Wollina *et al.*, 1991) [33, 126], respectively. The widespread distribution of VIM immune-staining in the epithelia, fibroblasts in papillary and reticular layers of the dermis and endothelia of the blood vessels supports the importance of VIM as cytoskeleton filament proteinas stated by Emam (2015) [46]. Melanosome was localized only in melanocytes existing among the cells of stratum basalis of the epidermis. There was a detection of over-expression of VIM and melanosome in the skin of camel than that of buffalo. More VIM content in the skin of camel may suggest higher filamentous proteins in the skin of camel than that of buffalo in addition to more pigmentation in the skin of camel, like other desert animals (El-Shafey *et al.*, 2017) [45]. The IHC findings of the normal canine skin detected both ck8-and 18 – expressions in the glandular epithelium of apocrine sweat glands, but not in myoepithelial cells. No immunoreactivity for ck8 and 18 were seen in sebaceous, hepatoid glands and in all epidermal layers. Single ck8expression was found in the outermost layer of the external root sheath at the isthmus and supra bulbar regions of the hair follicles and but the expression was less prominent compared to that of apocrine sweat glands (Kato *et al.*, 2007) [79]. All small arteries, arterioles, venules and capillaries present in the skin were stained with CD31, CD34, vWF, and Fli-1 in a similar pattern. Sometimes, hair follicle cells were positive for CD34. A reticular pattern of staining was seen with CD34 in the dermis, perhaps corresponding to CD34-positive mesenchymal cells (fibroblasts) and/or components of the extracellular matrix. Some lymphocytes present in the upper dermis and epidermis (granulation tissue) were also stained by Fli-1 (Pusztaszeri *et al.*, 2005) [103]. Keratinocytes (KC) were immunolabelled by two antibodies to human pan-keratin (AE1/AE3 & CK903) in both human and porcine skin. Basal KC was labelled by antibodies to keratins (K) 5/6 and K5/8, most likely reflecting the expression of K5. The cytoplasm of all suprabasal KC was labelled by the antibody to K1/10. The lectin Ulex Europaeus Agglutinin 1, recognizing alpha-L-fucose residues, stained the upper layer KC of porcine epidermis and the inner hair follicle sheath, as it did on human skin, but did not stain the porcine (apocrine) sweat glands (Debeer *et al.*, 2013) [39]. Merkel Cell (MKC) has been recognized with antibodies to K20 in porcine snout skin (Boulais *et al.*, 2009) and within hair-follicles (Smith *et al.*, 1998) [118]. In porcine skin, either in the epidermis or in the hair follicles, these antibodies have no reactivity (Debeer *et al.*, 2013) [39]. The antibody to S100 protein, that recognizes human Langerhans cells (LC) and melanocytes (Kanitakish, 2002), did not reveal appreciable reactivity on porcine epidermis. Porcine LC also expressed vimentin and Swine Leucocyte class II Antigens (SLA-II). The porcine homologue of the receptor Fc-gamma R IIIa/CD16 was inconsistently found on epidermal dendritic cells; it was expressed more weakly than on dermal dendritic cells. Overall, the distribution, density and phenotype of LC in porcine epidermis were found comparable to those of human LC (Debeer *et al.*, 2013) [39]. In both ewes and doe, IHC staining for CD3 positive 'T' lymphocytes revealed the presence of intraepithelial lymphocytes in Furstenberg's rosette CD3 positive 'T' lymphocytes were also localized within the lamina propria of mucosal folds involved in the formation of Furstenberg's rosette in teat (Asti *et al.*, 2011) [11].

Bone

Immunohistochemical staining (ABC method) noticed the distribution of Bone Morphogenetic Protein (BMP) along with collagen fibers of normal bone, in periosteal cells and in mesenchymal cells of marrow stroma while the bone cells of lamellar bone or in calcified bone matrix has little BMP. BMP plays an important role in bone fracture healing. BMP is found in the cytoplasm of tumor cells of osteosarcoma and chondrosarcoma. BMP monoclonal antibodies detect the BMP and inhibit the generation of new bone. This makes it potentially useful in diagnosing, treating, and providing a prognosis for osteosarcoma and other bone diseases. Special AT-rich sequence-Binding protein-2 (SATB2) is a sensitive and specific marker of osteoblastic differentiation in bone and soft tissue tumors. SATB2 has strong nuclear staining, seen in almost all cases of osteosarcoma (Conner and Hornick, 2013) [36]. As almost all other epithelioid bone and soft tissue tumors are negative formucins-4 (MUC4) marker, IHC for MUC4 can be helpful in its differential diagnosis with the exception of the glandular component of biphasic synovial sarcoma, though this tumor type is unlikely to pose diagnostic problems (Doyle *et al.*, 2012 and Tirabosco *et al.*, 2013) [42, 123]. Bone

marrow sinuses, characterized by a discontinuous Endothelial Cell (EC) lining, were positive for CD31, CD34, and vWF. Capillaries, venules and small arterioles present in the bone marrow in small amounts were also positive and did not show any significant differences for the above markers. Megakaryocytes were negative for CD34 but were strongly positive for vWF and CD31. Usually, myeloid and erythroid lineage cells were negative for the above markers, some cells occasionally being positive for CD31.A slight background staining was seen in some cases, especially with vWF. Fli-1 immuno-staining in the bone marrow did not show nuclear staining, presumably because of the decalcification process. Only in one or two cases, the nuclei of some megakaryocytes and of the myeloid lineage cells were positive (Pusztaszeri *et al.,* 2005) [103]. Lymph nodes sinusoidal EC of the marginal (subcapsular) and medullary sinuses were negative or focally and faintly positive for CD34 and vWF and was positive for CD31. In a case, sinusoidal EC of the marginal sinuses were positive for CD34 with the same intensity as for CD31. For CD31, CD34, and vWF, high endothelial venules were positive. In the lymph node capsule, a reticular pattern of staining was also seen with CD34, probably corresponding to CD34-positive mesenchymal cells. Sinus histiocytes were positive for CD31 but negative for CD34 and vWF because Fli-1 stained most lymphocytes present in the lymph node. Evaluation of EC staining was difficult, but EC at all levels seemed immunopositive for Fli-1 (Pusztaszeri *et al.,* 2005) [103]. Evaluation of lymphoid markers in lymphoid tissues showed $CD3^+$ cells in T-cell rich zones, $CD79a^+$ cells in B-cell rich and germinal center zones and $BCL6^+$ cells exclusively in germinal centers in pig (Meyerholz *et al.,* 2016) [93]

Digestive system

Using IHC, rats exhibited immunoreactivity for alpha-smooth muscle actin (alpha SMA), calponin and keratin 14 (K14), but not that for subunit of S-100 protein (S-100beta), vimentin and glial fibrillary acidic protein (GFAP) in the developing myoepithelial cells (MECs) of salivary gland. In the MECs, immunoreactivity for alpha SMA is appeared from the time when the microfilaments were initially deposited in these cells, i.e. at 20 days *in utero* in the sublingual and submandibular glands and at birth in the parotid gland. Immunoreactivity calponin was seen 1 day earlier than alpha SMA.A small number of the MECs expressed weak immunoreactive K14 from the time when the acinus-intercalated duct structure was established i.e. at 21 days *in utero* in the sublingual gland, at 5 days after birth in the parotid gland and after 5 weeks post-natally in the submandibular gland. Immunoreactivity to K14 was observed in the basal cells of the striated and excretory ducts (Ogawa *et al.,* 1999) [99]. Stimulate strongly the smooth musculature of the gut and secretion of the exocrine gland by serotonin (Fujita *et al.,* 1988; Furness and Costa, 1982) [54, 56]. The smooth muscle located in the mucosa of the glandular epithelium is contracted by the serotonin immunoreactive cells distributed in the gastrointestinal tract. These cells might control the secretion of mucous of the glandular epithelium too (Solcia *et al.,* 1987) [119] and the proportion of serotonin positive cells is relatively important. By IHC methods, regional distribution and relative frequency of endocrine cells were studied in fifteen portions of the porcine gastrointestinal tract. The first four cell types were marked over the other types and were numerous in the pyloric region than in the cardiac and fundic regions. The distribution of 5-HT-, somatostatin-, gastrin-, M-ENK-8--, motilin-, secretin-, cholecystokinin (CCK)- and gastric inhibitory polypeptide (GIP)-immunoreactive cells were wide and most numerous in the duodenum, while in the ileum, neurotensin- and glicentin-immune-reactive cells were predominant, in the small intestine. In the small intestine, rarely, glucagon- and BPP-immuno-reactive cells were seen.5-hydroxytryptamine-, somatostatin- and glicentin- immune-reactive cells were distributed widely in the large intestine and most numerous in the rectum. In the large intestine, motilin-, glucagon- and BPP-immuno-reactive cells were seen rarely (Ito *et al.,* 1987) [75]. The IHC method used seven types of antisera against serotonin, chromogranin, gastrin, cholecystokinin, somatostatin, glucagon and insulin. All over the gastrointestinal tract, chromogranin and serotonin immune-reactive (IR) cells were found. Conversely, in the oxyntic gland, pyloric gland and duodenum, only gastrin-IR cells were found, while cholecystokinin-IR and somatostatin-IR cells were detected in the oxyntic gland, pyloric gland and small intestines. Somatostatin-IR cells were also seen in the caecum. Glucagon-IR cells were found in entire parts of the gastrointestinal tract apart from the colon and rectum. No insulin-IR cells were found in the gastrointestinal tract of barking deer. In the small intestine, the cells were generally spindle shaped with long cytoplasmic processes ending in the lumen (open type), but they were occasionally spherical in shape (closed type) in the stomach and large intestine. An uncommon distribution pattern of endocrine cells in the gastrointestinal tract of the barking deer was noted for cholecystokinin- and glucagon-IR cells in barking deer (Adnyane *et al.,* 2011) [4]. Synaptophysin (SPY) - positive neuroendocrine cells were observed at 53 days of prenatal development (35% gestation) in goat (Garcia *et al.,* 2014) [57]. Similar results have also been reported for other ruminant species. In deer, neuroendocrine cells have been detected at 97 days (36% gestation) in the rumen and reticulum (Franco *et al.,* 2004) [52], and at an earlier stage of 67 days (26% gestation) in the omasum (Redondo *et al.,* 2005) [107]. In contrast, neuroendocrine cells are not found in sheep until 81 days (54% gestation) (Franco *et al.,* 2011 [108]; Redondo *et al.,* 2011 [49]; Franco *et al.,* 2012 [50]). In the recent investigation, immunoreactivity SPY was observed predominantly in the tunica muscularis and myenteric plexuses. While, a less immunoreactivity was found in the lamina propria-submucosa and serosa. Staining intensity increased significantly with gestational age as was previously noticed in sheep (Ceccarelli *et al.,* 1991) [23]. Non-neuronal enolase (NNE)-positive neuroendocrine cells were identified at a later stage than SPY-positive cells. The staining distribution and intensity patterns for the two factors were similar except that NNE staining was prominent in the epithelium of all forestomach compartments. GFAP-positive glial cells were identified at 68 days (45% gestation) in the rumen and at 64 days (43% gestation) in reticulum and omasum. A similar finding was observed in the rumen and reticulum of sheep and deer at 112 days (75% gestation) and 142 days (50% gestation), respectively (Franco *et al.,* 2011; 2012) [49, 50]. While, glial cells have been noticed at earlier stages in the omasum of sheep and deer (Redondo *et al.,* 2005; 2011) [107, 49]. Glial fibrillary acidic protein (GFAP)-positive staining was noticed in the lamina propria-submucosa, tunica muscularis, and serosa, and was particularly prominent in the myenteric plexuses. The presence of glial cells in the myoenteric plexuses and

submucosa has also been reported in sheep (Yamamoto *et al.*, 1995) [128] and cows (Teixeira *et al.*, 1998) [121]. In other species including rats (Nada *et al.*, 1988) [97], GFAP-positive cells have been detected in the ganglion at eplexuses. Glial cells are similar in structure and function to astrocytes of the central nervous system, and play a key role in controlling gastrointestinal functions and protecting enteric neurons (Abdo *et al.*, 2010) [3]. By VIM staining, glial cells were also detected. VIM positive reaction was observed in all fore-stomach compartments at 39 days of gestation. This result indicated that VIM is an earlier glial cell marker than GFAP and corresponds to observations reported during prenatal development of the sheep pineal gland (Franco *et al.*, 1997) [51] as well as the fore-stomach of sheep and deer (Franco *et al.*, 2011 [108]; Redondo *et al.*, 2011 [49]). At 39 days (25% gestation), immunoreactivity VIM was identified in pluripotential blastemic tissue and serosa. From 50 days of gestation, this immunoreactivity was distributed in the different tissue layers that were already differentiated. Positive reaction of VIM was observed in the same strata as GFAP staining. Peptidergic innervations markers identified in the goat fore-stomach have also been reported in lambs (Groenewald, 1994) [64]. In the present investigation, these factors were first observed in the reticulum and omasum, and later in the rumen. Similar findings have been reported for red deer in which these markers were detected at 142 days (50% gestation) in the reticulum (Franco *et al.*, 2012 [50]; 2004 [52]] and omasum (Redondo *et al.*, 2005; 2011) [107, 49], but not in the rumen until the perinatal stages (Franco *et al.*, 2004 [52]; 2011 [49]). Positive staining for NPY and VIP had a common pattern. For both makers, the myoenteric plexuses contained the greatest staining intensity. In lambs, NYP-positive staining in the myoenteric plexuses has low to moderate intensity while that for VIP is more intense (Groenewald, 1994) [64]. In contrast, high density immunoreactivity for VIP is mostly marked in the smooth muscle layers of the reticular groove, reticulum and rumen of cattle (Kitamura *et al*., 1986) and omasum of sheep (Yamamoto *et al.*, 1995) [128]. Peptide distribution observed in both the present investigation and earlier studies (Kitamura *et al.*, 1993; 1986) [81, 82] indicates that peptide-containing nerve fibers are mainly intrinsic in origin and derived from the intramural ganglia of the fore-stomach wall. The muscularis mucosae showed immunoreactivity for both alpha Smooth Muscle Actin and gamma Smooth Muscle Actin. While, the condensed fibrous layer appearing between the propria mucosa and tela submucosa was only immunoreactive for alpha-SMA except for that in the goat and Barbary sheep reticulum which is intermingled with gamma-SMA immunoreactivity. In ruminant species the distribution of muscularis mucosae and/or condensed fibrous layer differs among the compartments of fore-stomach and in the rumen, only the condensed fibrous layer was identified (Kitamura *et al.*, 2003) [83]. Immunohistochemically, the β-cells were spread in different areas of the islets in both animals (camel and buffalo). Glucagon hormone, the amount and intensity in the pancreatic islets of the buffalo were higher than that in the pancreatic islets of the camel. In contrast, the insulin hormone was higher in amount and intensity in the camel than in the buffalo. The α-cells distribution at the periphery of the pancreatic islets in both animals; the amount of insulin hormone was higher in the pancreatic islets of the camel than that of the buffalo. Both α- and β-cells in the camel and buffalo were observed outside the pancreatic islets in the connective tissue (Bargooth *et al.*, 2020) [14]. Immuno histochemical observations revealed detection of ki-67 immuno staining in the ruminal epithelium only which is in accordance with Blättler *et al.*, (2001) [18] in calves. The limitation of Ki-67 immuno staining to the epithelium basal cells layer refers to starting of keratin biosynthesis in the basal cells. In addition, ki-67 in basal cells assists the permanent renewal of the epithelial cells that was supported by Bjerknes *et al.*, (2005) [17] and Conto *et al.*, (2010) [37]. On the other side, immune staining detection of caspase3 in the cells of spinous layer indicates the process of apoptosis that will substitute from the proliferation of basal cell layer. Localization of caspase3 in the cornified epithelial cells that referred to the continuous tearing of the keratin layer of ruminal epithelium. This finding was similar to that of Gui *et al.*, (2016) and Xu *et al.*, (2018) [67, 127] who studied the apoptosis of ruminal epithelium in goat and sheep, respectively. In recent studies, vimentin immune stainings were identified in boundaries of the intercellular spaces and some spinous cells in the ruminal epithelium. On contrary, vimentin was not seen during prenatal life in stomach of goat (Garcia *et al.*, 2014a and b) [57, 58]. In addition, vimentin was not recorded in endothelia of blood vessels in rumen in the earlier studies during prenatal life in goat (Garcia *et al.*, 2014a and b) [57, 58]. Vimentin act as cytoskeleton protein may be associated with postnatal life to support the cells of rumen and to support the organelles in cytosol of cells (Katsumoto *et al.*, 1990) [80]. Fibroblasts in lamina propria-submucosa of rumen of Baladi goat showed vimentin immune reactivity that was similar to findings of Ikemizu *et al.*, (1994) [73] in the bovine rumen. Vimentin immunostaining in glial cells of myenteric plexuses of rumen that was in accordance with findings of Garcia *et al.*, (2014a and 2014b) [57, 58] in goats. Teixeira *et al.*, (1998) [121] also, in bovine reticulum, described immune reactivity for glial cells in the reticular folds. Glial cells identified in rumen of Baladi goat supports the important role of glial cells as non-neuronal elements of the enteric plexuses in regulation of GIT functions and protecting enteric neurons (Abdo *et al*., 2010) [3]. CD3+lymphocytes were rare in the infiltration surrounding the acute migratory tracts, suggesting inhibition of the local cell-mediated immune response. Goats with numerous hepatic calcareous granulomas showed the most severe hepatic damage, including marked cirrhosis, with a striking infiltrate of CD3+ T lymphocytes and lambda IgG^{+}plasma cells, replacing extensive areas of hepatic parenchyma, in which hypertrophy of the smooth endoplasmic reticulum of hepatocytes was evident (Perez *et al.*, 1999).

Liver sinusoidal Endothelial Cell (EC) continuously expressed CD31 from the portal space to the centrolobular vein. In contrast, CD34 was expressed only in the periportal area, the centrolobular sinusoids being mostly negative. Expression of vWF was similar to that of CD31. Fli-1 usually stained the nuclei of EC present in the sinusoids; portal vein, centrolobular vein, and hepatic artery. A granular cytoplasmic reactivity was also occasionally seen in hepatocytes (Pusztaszeri *et al.*, 2005) [103].

Spleen

Spleen sinusoidal Endothelial Cells were diffusely positive for CD31 but negative for CD34. In the red pulp, CD34 only marked the capillaries. VWF staining was similar to that for CD31 but was slightly less intense. There were similarities in the staining pattern of the central veins, arteries and other

vessels present in the spleen.Fli-1 stained the nuclei of EC present in the sinusoids and also the lymphocytes present in the white pulp. The larger vessels which comprised the central arteries were also stained (Pusztaszeri *et al.,* 2005) [103]. The goat spleen is having higher expression of MT1 (Melatonin) receptor on the splenocytes particularly in red pulp region. But, the translucent white pulp region is having less expression of MT1 or MT2 receptors (Ghose *et al.,* 2015) [59]. Immunohistochemical studies revealed that CD3 positive T-lymphocytes were recognized as brown coloured cells. In the inter-follicular region, CD3 positive T-lymphocytes were found to be more. A similar observation was noticed by Bozkurt and coworkers (2018) [19] in hemal nodes of deer and Ceccarelliand associates in 1986 in sheep and cow. Very few T-lymphocytes were seen within the lymphoid follicle and found to be more around the margin of lymphoid follicles as per in dromedary camel. However, Casteleyn *et al.,* 2008 contradicted these findings and observed the existence of more number of T-lymphocytes in the germinal centre of lymphoid follicles. It was detected that CD79a positive B-cells were found to be more at the mantle zone of lymphoid follicles. A similar observation was reported by Yoon *et al.* (1989) and Bozkurt *et al.* (2018) [132, 19] in goat (hemal node). In the IHC staining technique strong positive reaction for cytoplasmic IgG bearing B- lymphocytes was detected within the germinal centre of lymphoid nodules, towards the base of the FAE and some cells even infiltrated the crypt epithelium. In the mantle zone and internodular area, reaction was very mild showing that T- lymphocytes predominated in these areas (Indu *et al.,* 2018) [74]. The thymus was having a high expression of MT1 receptor and this receptor was cosmopolitan in distribution over the entire structure. The Hassel's corpuscles and the PALS were having more distribution of this receptor. Even though, the macrophages which were present in the Hassel's corpuscles were also having this receptor (Ghose *et al.,* 2015) [59].

Respiratory system

Immunohistochemistry was used to distinguish large-cell carcinoma from malignant pulmonary histiocytosis. Tumor cells have strong immunoreactivity for cytokeratin, consistent with epithelial origin. However, a major percentage of the neoplastic cells co-expressed MHC-II and vimentin. The type II alveolar epithelial cell was considered to be the cell of origin of the neoplasm depending on the presence of lamellar bodies in some neoplastic cells and immunoreactivity for surfactant protein A and thyroid transcription factor-1 (Buendia *et al.,* 2008). Immunohistochemical method using primary antibody calcium channel, voltage dependent, gamma subunit 5 (CACNG5) and secondary antibody one-step HRP polymer anti- mouse, rat and rabbit IgG (H+L) with DAB exhibited results approximately similar to that of histological studies, when tumor appeared in the upper part of the trachea without any indication of calcification (Al-Badri and Al-Salman, 2016) [7]. Capillaries in the alveolar wall steadily stained for CD31 and CD34 but were usually negative for vWF. Alveolar macrophages were negative for CD34 and vWF but were positive for CD31 with a membranous pattern of staining. The nuclei of EC of the different vessel types in the lungs were diffusely stained by Fli-1.The nuclei of lymphocytes as well as the cytoplasm of some alveolar wall cells probably corresponding to mastocytes were also stained (Pusztaszeri *et al.,* 2005) [103].

Cardiac system

The intramyocardial capillaries staining pattern was different between CD31 and CD34. Immunoreactivity of CD34 was seen in more capillaries than CD31. The staining pattern of vWF was similar to that for CD31. Imunostaining for CD31 was strong for endothelium but for CD34 and vWF, it was irregular and less intense. Immunostaining for CD34+was seen for fat tissue capillaries. Endothelial cells stained with Fli-1 were present in interstitial capillaries, arterioles and venules in the myocardium. A diffuse cytoplasmic background staining of cardiomyocytes was also seen with Fli-1 immunostaining (Pusztaszeri *et al.,* 2005) [103]. Antibody 445-6E10 was selected for its specific and homogeneous staining of the cytoplasm of the Purkinje fibers of the ventricular conduction system of the bovine heart (Oosthoek *et al.,* 1993) [101]. Intercalated discs are made up of a protien named Desmin. It is the main component of the cardiomyocyte cytoskeleton and forms the intermediate filament. Because of its role in the formation of striation within the myocardium, Desmin plays an important part in the normal functioning of the myocardium. The structure of cardiomyocytes is compromised and there is a disorganization of Desmin filaments and loss of cross striation in the course of heart failure (Sharov *et al.,* 2005 [115]; Gofflot *et al.,* 2008 [61]). Vimentin builds intermediate filaments of mesenchymal cells in fibroblasts, macrophages, endothelial cells and smooth muscle cells. In normal cardiac tissue, Vimentin positive cells are distributed among cardiomyocytes, forming a delicate stroma, the amount of which increases with progressing heart failure (Hein *et al.,* 2000 [70]; Sharov *et al.,* 2005 [115]). Along with heart failure, the structure of cardiomyocytes and intercalated discs undergoes disorganization, which leads to loss of myofilaments and their supporting proteins e.g. Desmin (Schaper *et al.,* 2002 [113]; Sharov *et al.,* 2005 [115]). Cardiomyocyte remodelling is accompanied by the expansion of interstitial tissue with scar formation and fibrosis (Schaper *et al.,* 2002) [113]. The interstitial tissue in failing hearts contains not only of mesenchymal cells, but also collagens and fibronectin (Sharov *et al.,* 2005) [115]. That may explain why we did not find a correlation between interstitial fibrosis and the percentage of vimentin-positive cells although the number of those cells was the highest in the DCM group. The periostin activates cardiac fibroblasts, influencing their migration and trans-differentiation (Frangogiannis, 2012) [53]. According to (Zhao *et al.,* 2014) [133], the increase in interstitial periostin expression shows a high correlation to heart fibrosis. When both interstitial and cardiomyocyte periostin expression were evaluated and no such relationship was found. But, both greater interstitial fibrosis and more pronounced change in the periostin expression pattern were found in the DCM group than in the Myxomatous mitral valve disease (MMVD) group. The Caspase-3 lower expression was detected in the DCM group as compared to the MMVD and the control group. This contradicted the results of other authors. In tachycardia-induced heart failure, an increased expression of Caspsase-3 genes was observed (Mahmoudabady *et al.,* 2013 [90]; Heinke *et al.,* 2001 [71]). In collagen-rich connective tissue subjected to mechanical stress e.g. heart valves, Periostin expression is specifically high (Frangogiannis, 2012) [53]. During heart failure, the Desmin, Vimentin, Periostin and Caspase-3 expression pattern modify in the left atrium, regardless of the cause. These alterations are more marked in dogs with DCM than in dogs with MMVD and similar left atrial enlargement,

indicating that volume overload may not be the only cause of myocardial changes in DCM (Alroy *et al.*, 2000) [9].

Kidney

In normal canine kidneys, the visceral glomerular epithelial cells (podocytes) expressed only Vimentin, and Cytokeratin was found exclusively in parietal glomerular epithelial cells. In kidney of dogs, epithelial tubular cells lose their cytokeratin staining characteristics and transdifferentiate into cells exhibiting a key mesenchymal feature of Vimentin-positive staining in glomerulonephritis (Aresu *et al.*, 2007) [10]. Cytokeratin showed very intense expression in transitional epithelium lining of renal calyxes while its strong or weak expression was found in epithelium lining of distal tubules, loop of Henle and strong expression in endothelial cells. Weak expression of cytokeratin was observed in collecting tubules whereas epithelial cells of proximal tubules and glomerulus were negative. Immune expression of Vimentin was present in the cells of mesenchymal origin. It has strong expression in interstitial tissue and mesangial cells of glomeruli. Very strong expression of Vimentin was seen in epithelial cells of distal tubules (Laszczyńska *et al.*, 2012) [86]. In Syrian hamsters, IHC findings indicate that the estrogen-induced renal tumor has an embryonal origin and the presence of cytokeratin, desmosomes, microvilli, and cilia indicates its epithelial nature (Gonzalez *et al.*, 1989) [62]. Immunohistochemically, the atypical tumorous cells appeared moderately to highly reactive to Ki-67, a nuclear proliferation marker while there is a marked reactivity to cytoplasmic cytokeratin 7 (CK7) and low to poor reactivity towards cytokeratin 20 (CK20) in abnormal transitional epithelium and invasive cell nest (Deshmukh *et al.*, 2010) [40]. In humans, the fenestrated endothelium of the glomeruli strongly expressed CD31 and CD34 regularly but it was only focally positive or completely negative for vWF. When the kidneys from hypertensive patients were immune stained, the glomeruli were weakly or moderately positive for vWF as compared to the kidneys from patients without hypertension (Pusztaszeri *et al.*, 2005) [103]. In Indian water buffalo, the CK7 immunostaining was noted in all layers of transitional epithelium and generally, the top most umbrella cells displayed prominent and diffuse immunostaining, while the basal cell layer revealed proportionally moderate immunoreactivity. In this study, a low or poor and focal loss of reactivity to CK 20 by the superficial uroepithelial cells suggest the possible loss of elasticity and permeability function of urinary bladder and membrane turnover process, therefore leading to an *in situ* rupture and accumulation of urine in abdominal cavity.

Reproduction

Both repeat breeder and anestrous buffaloes and cows showed significant ($p < 0.01$) low serum levels of Ca and 25(OH)D as well as P4 and E2 in comparison with normal cyclic animals. Immunohistochemically, CaBP-9k and VDR (vita D receptor) immunoreactions were limited to the endometrial epithelia of all examined animals. But, both repeat breeder and anestrus buffaloes and cows showed remarkable lower uterine expressions for CaBP-9k and VDR in comparison with normal cyclic ones (Emam and Gad, 2020) [47]. Follicular stimulating hormone receptor (FSHR) was abundantly localized in the membrane and the cytoplasm of the granulosa cells of Egyptian buffalo during follicular phase. Similar observations were seen in granulosa cells of growing follicles in human (Meduri *et al.*, 2002), Indian buffalo (Sharma *et al.*, 2011) [114] and pig (Durlej *et al.*, 2011) [44]. In the cytoplasm of theca cells, moderate FSHR positive immunostaining was also observed. Similarly, in horse, Scarlet *et al.*, (2015) [112] also recorded moderate FSHR localization in the same cells. These results indicated that FSHR and its ligand (FSH) are necessary for follicular growth. Thus, it can be concluded that the existence of FSHR in buffalo granulosa cells underlie the mechanisms for growth, differentiation, recruitment and selection of follicles. The luteal tissues (endothelial cells, large and small luteal cells and septa of connective tissue capsule) showed weak to very weak FSHR immunostaining. These findings come in consistence with Scarlet *et al.* (2015) [112] who found weakly stained luteal cells with FSHR immunostaining in mare. Likewise, at mRNA level, FSHR was over-expressed during the follicular phase but was down-expressed during the luteal phase to levels below that of the control (non-cycling) animals. In human (Minegishi *et al.*, 1997) [94], cat (Saint-Dizier *et al.*, 2007) [110], bovine (Rajapaksha *et al.*, 1996) [105] and rat (Camp *et al.*, 1991) [20], similar low luteal expression of FSHR was also seen. The immunolabelling of AE1/AE3 (anionic exchanger 1) in granulosa cells (GC) was strongest in the early follicle stage and gradually decrease when the follicle reaches the Graafian follicle stage. As there is development from stage I to stage III, its immunolabelling increased. The immunolabelling of inhibin alpha was inversely proportional to that of AE1/AE3 in the progressing ovarian follicles as their immunolabelling is opposite to each other during folliculogenesis. Anti-Müllerian hormone (AMH) was immune-positive in almost all granulosa cell stages in different intensities and percentages, except for some negative staining in the atretic stage IV follicles (Teh *et al.*, 2018) [120]. The goat ovary was having high expression for both the melatonin receptors (MT1 and MT2). A high expression pattern for MT1 receptors in thecal and granulose cells was found but the MT2 receptors were most abundantly present in thecal cells as well as on the cumulus oophorous layer of goat ovary surrounding the ovum. In goat uterus, high expression of both the membrane bound melatonin receptors (MT1 and MT2) was detected. However, the MT1 was highly expressed only on the membranes of secretory cells of endometrium but MT2 was highly expressed on both, the non-voluntary muscle cells of myometrium and on the secretory cells of endometrium (Ghosh *et al.*, 2015) [59]. In the various cell types of the canine uterine horns, body and cervix, immunohistochemical studies are helpful in describing the normal distribution of progesterone receptors. Nuclear staining for progesterone receptors was observed in epithelial cells of the surface epithelium, glandular ducts and basal glands of the endometrium, in endometrial stroma cells and in myometrial smooth muscle cells. This staining was positively correlated with the estradiol-17 beta: progesterone ratio and indicates the positive effect of estradiol-17 beta and the negative influence of progesterone on the receptors. Staining scores were high during pro estrus periods and decreased during estrus to early met estrus period. Staining scores of the smooth muscle cells and stromal cells increased again in late met estrus. In anestrus, high scores of the surface-epithelial cells contrasted with minimal scores of the basal glands (Vermeirsch *et al.*, 2000) [124]. In canine, expression of estrogen receptors(ER) was performed by an indirect immunohistochemical technique with monoclonal antibodies. Estrogen receptors were found as a red nuclear staining in the surface, crypt, endometrial

stromal cells, glandular epithelium and in smooth muscle cells of the tunica muscularis of the uterus. The total scores of ER-positive cells varied During the estrous cycle, where the highest scores was in early proliferative stage and the lowest scores in the early secretory stage of the estrous cycle (cock *et al.*, 1997) [34]. Primary antibodies in opposition to angiotensin changing enzyme (ACE), S-100, galactosyltransferace (GalTase), connexin 43 (Cx43), alpha easy muscle actin (α-SMA) and vascular endothelial boom factor (VEGF) had been used for IHC research in males. Immunohistochemical research confirmed that apart from VEGF which reacted negatively, all antibodies used confirmed variable reactivity withinside the extraordinary epididymal structures. Apical cells expressed a strong reaction with ACE along the full length of the duct. The principal cells in the caput epididymis exhibited a distinct reactivity with GalTase and S-100. The peritubular muscular coat expressed a prominant immunostaining for Cx43 and for α-SMA in buffalo (Alkafafy *et al.*, 2011) [8]. Immunoreactive androgen receptor is mainly found in luminal and glandular epithelia of the pig uterus and to a lesser amount in the myometrium and does not change significantly during the estrous cycle or early pregnancy. Exhibition of the androgen receptor gene in the pig endometrium and myometrium appears to be regulated by E(2) and progesterone(Cardenas and Pope, 2003) [22].

Brain

Lysozyme is widely used as a histiocytic marker in both human and animals to substantiate a diagnosis of histiocytic disorders. In human histiocytic disorders, the tumors that originated from macrophage lineage exhibited high expression of lysozyme, whereas those arose from dendritic cell had low expression or devoid of this molecule (Beckstead *et al.*,1984 [15]; Mason *et al.*, 1975 [91]; Moore *et al.*, 1986 [95]; Yang *et al.*, 2010) [129]. Inducible nitric oxide synthase (iNOS) and dendritic cell-lysosomal associated membrane protein (DC-LAMP or CD208) were employed as macrophage and dendritic cell markers, respectively (Thongtharb *et al.*, 2016) [122] to diagnose these disorders.

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