INTERNATIONAL JOURNAL OF AGRICULTURE & BIOLOGY
ISSN Print: 1560–8530; ISSN Online: 1814–9596
24–0351/2025/33:330109
http://www.fspublishers.org

Review Article

Potential Interaction between Inflammation and Tumor Microenvironment

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Received 12 August 2024; Accepted 17 September 2024; Published online 07 December 2024

Editor: Zafar Iqbal

Abstract

The intricate relationship between inflammation and cancer is a well-established paradigm in oncology. Inflammation is recognized as one of the key hallmarks of cancer, profoundly influences tumor progression, malignant transformation, and the efficacy of chemotherapy. The tumor microenvironment, comprising various factors and signaling mechanisms, plays a pivotal role in shaping the biological characteristics of tumors. This review delves into the components of the tumor microenvironment, including inflammasomes, cytokines, and non-coding RNA, elucidating the impact of inflammation on tumor microenvironment dynamics throughout tumorigenesis. Particularly, inflammation exerts its influence by inducing immune suppression, with acute inflammation paradoxically fostering anti-tumor immune responses. The interplay of inflammatory factors significantly regulate immune responses within the tumor microenvironment, involving inhibiting immune cell activity, allowing tumors to evade surveillance, and promoting their proliferation and metastasis. Moreover, inflammation contributes to oxidative stress, generating reactive oxygen species and reactive nitrogen species. These oxidative agents can inflict damage on proteins, lipids, and nucleic acids, inducing genetic mutations and neoplastic transformations. Non-coding RNA molecules, crucial players in the tumor microenvironment, significantly contribute to the regulation of tumors and inflammation through diverse pathways. A comprehensive understanding of the interplay between inflammation and the tumor microenvironment holds immense potential for advancing cancer research and developing novel treatment strategies. This review provides a theoretical foundation for combating tumors by exploring the nuanced connections among inflammation, tumor microenvironment, and cancer development.

Keywords: Tumor; Inflammation; Tumor microenvironment; Circular RNA

Introduction

There has always been a connection between inflammation and tumors. When a French surgeon, Jean Nicholas Marjolin discovered that squamous cell carcinoma would appear near burn scars, describing them simply as ulcers; by 1863, the German Doctor Rudolf Virchow first pointed out the interconnection between cancer and inflammation, and he found a large number of inflammatory cells in cancer specimens, proving that chronic inflammation sites can provide a good starting environment for the occurrence and development of cancer. In recent years, with the deepening of research on inflammation and cancer, Hanahan and Weinberg (2011) believe that some inflammation can enhance the occurrence and progression of cancer. Inflammation that promotes cancer is also considered to be one of the other characteristics of cancer; inflammation is considered to be related to various aspects of tumor occurrence, development, malignant transformation, invasion and metastasis. Chronic inflammation provides a favorable environment for tumor occurrence and metastasis by inducing immune suppression (Briukhovetska *et al.* 2021). At the same time, the inflammatory response triggered by tumors promotes cancer by blocking anti-tumor immunity, remodeling the tumor microenvironment (TME) and directly acting on cancer cells (Greten and Grivennikov 2019; Wajid *et al.* 2022). Acute inflammation can generate anti-tumor immune responses by promoting the maturation and function of dendritic cells and activating effector T cells, thereby promoting the formation of a tumor-suppressive environment. In addition, acute inflammation may also promote cancer cell apoptosis in different types of cancer (Piotrowski *et al.* 2020; Wajid *et al.* 2022; Lochi *et al*. 2023). Further study of the process by which inflammation interacts with the TME may help improve cancer treatment and diagnosis. This review will delve into

To cite this paper: Tunio S, PK Siyal, MK Menghwar, M Memon, H Tunio, MA Memon (2025). Potential interaction between inflammation and tumor microenvironment. *Intl J Agric Biol* 33:330109. https://doi.org/10.17957/IJAB/15.2255

the critical role of the interplay between inflammation and the TME in cancer development, progression, and metastasis. By analyzing this complex interaction, we hope to provide new ideas and strategies for cancer prevention and treatment. According to current relevant research progress, there is a direct fundamental connection between carcinogenesis and inflammation. According to relevant literature reports (Onuma *et al.* 2015), 15~20% of cancer-related deaths are related to pre-existing inflammation. Some chronic inflammatory diseases, such as between hepatitis and liver cancer, or chronic infection or inflammation triggered through environmental exposure such as smoking or asbestos, increase the hazards of cancer (Würtz *et al.* 2020). Furthermore, the use of NSAIDs reduces the risk of various tumors and reduces mortality (Vidal *et al.* 2015), further emphasizing the role of inflammation in neoplastic transformation. Numerous studies have revealed that chronic infection is narrowly related to the majority of cancer-related deaths. A classic example is hepatitis caused by hepatitis B and hepatitis C viruses. If patients suffer from this disease for a long time and it is not eradicated, it may lead to the occurrence of liver cancer in the future. Some non-infectious causes may also lead to inflammation and cancer. For example, cancers such as esophageal cancer, pancreatic cancer, and gallbladder cancer are caused by inflammation of organs such as esophagitis, chronic pancreatitis and cholecystitis (Lin *et al.* 2014; Memon *et al.* 2016). Inflammation promotes the occurrence and development of cancer in many ways.

Tumor microenvironment (TME) and inflammation

TME refers to a complex and rich environment composed of multiple cells, which plays a significant role in the development and growth of tumors. The TME includes primary tumor cells, various tissue cells (such as endothelial cells and fibroblasts), various immune cells, adipocytes and extracellular fluid. These diverse compositions make the TME a highly complex local environment. The TME is an important component of tumor growth and progression, has an important impact on the growth, metastasis and drug resistance of tumor cells (Ujjan *et al.* 2021; Shi *et al.* 2022). Immune cells performance an vital role in the TME, including inhibiting or promoting tumor growth and playing a key role in host immune investigation and removal of new cancer cells (Finn 2018), stromal cells and secreted molecules can affect the production and migration of tumor cells (Choi *et al.* 2021; Ali *et al.* 2023a, b, c). Number of studies have revealed that the TME can determine the function of abnormally growing or developing tissues in the body and shows a key role in the further evolution of these tissues into malignant tumors (Mroue and Bissell 2013). Changes in the TME have an important impact on tumor occurrence and development. The components and composition inside the TME change during different growth stages, and these changes can lead to metabolic reprogramming of immune cells and thereby change their functions (Vistro *et al.* 2020; Ning *et al.* 2021). Furthermore, the TME also affects immune response and tumor adaptation. The growing environment plays a certain role. Studies have shown that changes in the TME can cause immune cells to change their functions and reduce their killing effect on tumor cells, thus promoting tumor growth. This process may lead to immune escape of tumors and increase their resistance to immunotherapy (Arbab *et al.* 2020; Jones *et al.* 2020). The remodeling of the TME has an important impact on tumor development and can regulate the metabolism and function of immune cells to shape a microenvironment suitable for tumor growth to promote tumor production and invasion, metastasis, angiogenesis and immune escape (Jiang *et al.* 2019; Malyar *et al.* 2021). In the past few years, over the past decade, research on the TME has impacted our understanding of cancer evolution, and treatment strategies have gradually shifted from a tumor-centric approach to the management of the tumor ecosystem. The communication between inflammation and the tumor microenvironment can promote the development of tumors. This conclusion has been extensively studied and proven. There are multiple ways to achieve the interface between inflammation and the tumor microenvironment. First, inflammation can cause cells in the tumor microenvironment to produce inflammatory mediators, such as cytokines and chemokines, which can affect the proliferation and invasion capabilities of tumor cells. Studies have confirmed that compared with normal tissues, cytokines such as interleukin β (IL) 1β, IL-6 and tumor necrosis factor α (TNF-α) are significantly increased in tumor tissues (Qeadan *et al.* 2020); Secondly, inflammation can also stimulate the activation and infiltration of immune cells in the tumor microenvironment. These immune cells can release anti-tumor factors, such as natural killer cells and T cells, which inhibit tumor initiation and progression. Such as T cells and tumor-associated macrophages, which can promote tumor growth and immune evasion (Triner and Shah 2016; Ayoob *et al.* 2021). In addition, inflammation can also change the extracellular matrix in the tumor microenvironment, making it more conducive to the growth and migration of tumor cells (Vadovics *et al.* 2022). The interplay between inflammation and the tumor microenvironment has important clinical implications for tumor development and progression. Therefore, the interface between inflammation and the tumor microenvironment is one of the important areas of tumor research. In-depth understanding of the mechanism and influencing factors of this interaction is of great significance for the development of new tumor treatment strategies.

Immune cells and inflammation

Immune cells not only play a huge role in inflammation, but also affect the occurrence of tumors (Fig. 1). In many tumors, immune cells are the most abundant non-cancer

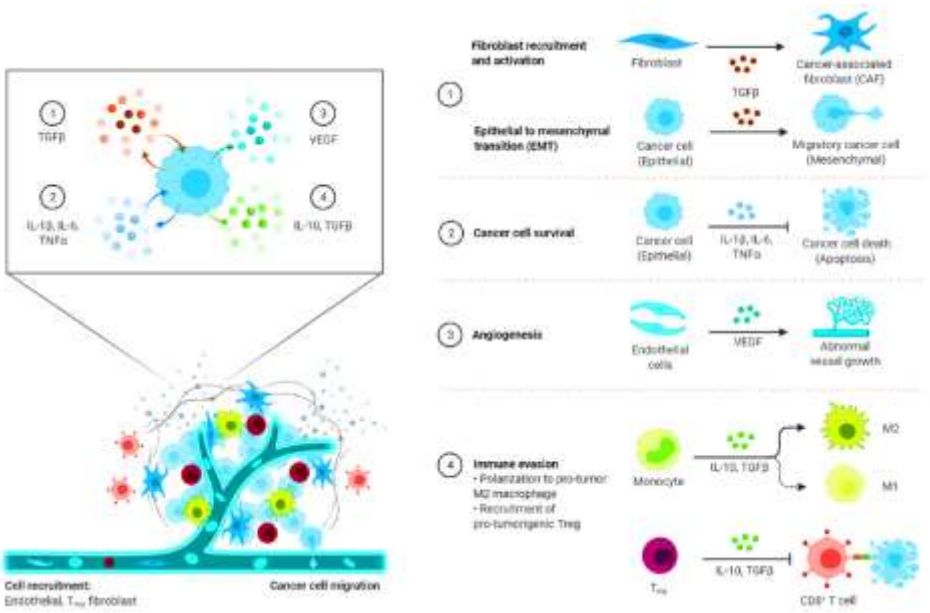

Fig. 1: Different immune cells are the most abundant non-cancer cells in the TME

cells in the TME, including different innate immune cells; in the TME, the cells most actively involved in regulating tumor progression are myeloid-derived suppressor cells, natural killer cells, macrophages, neutrophils, dendritic cells, and monocytes (Banchereau *et al.* 2000; Duan *et al.* 2023a, b; Azhar *et al.* 2023). T cells are key regulators of anti-tumor function, and their recruitment and activation greatly increase the healing potential of immunotherapy by utilizing activated T cells to kill different tumor cells (Waldman *et al.* 2020). Once dendritic cells appear functional Therefore, dendritic cell dysfunction in tumors is related to tumor progression; the role of natural killer cells in tumor immune surveillance has been fully confirmed and it is considered to be involved in the clearance of tumor cells at the primary site and tumor cells at distant sites (Waldhauer and Steinle 2008; Sun *et al.* 2024a, b). Tumor-associated macrophage (TAM) is an important type of immune cell in the TME. Its main function is to remove pathological cells and inflammatory mediators, participate in inflammation regulation and immune response, and the transformation process of M1 macrophages. Mainly regulated by inflammation (Zou *et al.* 2020). When an inflammatory response occurs in the body, macrophages are converted from M0 type to M1 type. This transformation process is mainly regulated by a variety of signaling pathways, including the nuclear factor kappa-B (NF-kB) signal transduction pathway and signal transduction and STAT3 signaling pathways. M2 macrophages are a macrophage subtype with immunosuppressive and tumor-promoting properties. They can produce a variety of anti-inflammatory factors, such as IL-10 and transforming growth factor-β (TGF) to inhibit immune responses and promote the growth and spread of tumor cells (Shima *et al.* 2020; Sun *et al.* 2023a, b). The transformation process of M1 macrophages into M2 macrophages is closely related to the mediation of inflammation. Inflammatory factors can activate a variety of signaling pathways, such as signal transducer and activator of Transcription6 (STAT6) signaling pathway and the Toll-like receptors (TLR) signaling pathway, thereby promoting the transformation of M1 macrophages into M2 macrophages (Yi *et al.* 2020; Zhu *et al.* 2023).

Inflammation can affect the occurrence and development of tumors by affecting the biological behavior of immune cells, mainly by changing the secretion of immune cells (Ahmed *et al.* 2018; Xu *et al.* 2021). For example, immune cells release different inflammatory mediators and cytokines, such as IL-1, TNF-α, IL-6, *etc*. Excessive release of these molecules can lead to the occurrence and persistence of inflammatory responses in the TME, thereby affecting tumor growth and metastasis. Therefore, in order to explore the mechanism of these excessively released cytokines and inflammatory mediators in promoting tumor growth, we can try to explore new tumor treatment options; at the same time, we can try to control inflammation to affect tumor progression. Further study of the interaction mechanism between inflammation and immune cells and their impact on the TME has great potential value in the treatment of tumors.

Stromal cells and inflammation

Stromal cells in the TME also play an essential role in the development of tumor growth. Stromal cells are a type of cells with diverse functions, including endothelial cells, cancer-associated fibroblasts (CAFs), and other cells. Their

main role is to maintain the structural integrity and functional balance of tissues. In tumors, the number and activity of stromal cells increase significantly, which is consistent with tumor cells. Forming a complex interaction network (Spary *et al.* 2014; Haseeb *et al.* 2019a, b). Fibroblasts are the most abundant stromal cells in the human body. Their role is to promote the growth and spread of tumors by secreting cytokines, growth factors, and chemokines, and remodeling the extracellular matrix (ECM) (Shi *et al.* 2020; Joshi *et al.* 2021; Zhu *et al.* 2023). CAFs, which are activated fibroblasts seen in the tumor stroma, have been connected to the development of tumors and the aggressiveness of cancer. It has been discovered that CAFs encourage unchecked development, angiogenesis, invasion, metastasis, and resistance to therapy. CAFs are a component of the stroma that surrounds the tumor microenvironment (TME) and they secrete growth factors, cytokines and chemokines, as well as modify the extracellular matrix, to facilitate tumor development. It has been shown that interactions between tumor cells and CAFs can activate CAFs, which then allows tumor cells to take advantage of the growth factors and cytokines that CAFs emit. This can have pro-tumor consequences. Studies have confirmed that CAFs can secrete a variety of factors, such as hepatocyte growth factor (HGF), chemokine SDF-1 (stromal cell-derived factor 1), IL-1β, platelet-derived growth factor (platelet derived growth factor (PDGF), homologous phosphatase and tensin homolog (Pten) and human recombinant Sonic hedgehog (Shh) *etc*. (Togo *et al.* 2013). There is a complex interaction between stromal cells and inflammation. The two influence each other and jointly participate in the occurrence and development of tumors. CAFs have different subpopulations in different tissues and organs and can mediate different pathological reactions. Some studies have found that there are cancer-related CAFs groups with different functions in different cancers (Öhlund *et al.* 2017; Ran *et al.* 2023). In the TME, the biology of CAFs, CAFs can help the growth and development of malignant tumors through a series of biological behaviors such as promoting angiogenesis, forming fibrotic matrix, mediating metastasis and regulating immune infiltration (Davidson *et al.* 2021). The occurrence of inflammation is inseparable from CAFs, which serve as immunomodulators. At the same time, CAFs can also help clear the inflammatory response. Therefore, there is an interrelationship between inflammation, CAFs and tumors in the TME. Further study of their specific interaction mechanisms will help Understanding the impact of the three on the occurrence and development of tumors. In addition, in-depth research on CAFs in the TME will help to play the role of CAFs in tumor treatment. For example, CAFs can stimulate inflammatory responses and promote anti-tumor immunity.

Extracellular matrix and inflammation

The ECM also plays a huge role in tumor development in the TME. ECM is a complex network structure composed of a series of proteins and polysaccharides. It not only provides cell support and structure, but also participates in cell growth, differentiation and migration by interacting with receptors on the cell surface. There is an imbalance between the synthesis and degradation of various substances in the ECM, involving machinery, metabolism and inflammation and many other factors (Palmer *et al.* 2013; Duan *et al.* 2023a, b). However, when the ECM interacts with inflammatory processes, it can have an important impact on tumor initiation and progression. Inflammation is a physiological response of the body to injury or infection. The interaction between ECM and inflammation is a complex process, which involves the interaction of multiple cells and molecules, including the degradation of ECM, the migration of inflammatory cells, and inflammation release of factors, *etc*. The ECM plays a key role in tumor development and progression. Its primary role is to influence the development process of tumors by regulating the proliferation and differentiation of tumor cells. Studies have shown that the components and structure of ECM can regulate the proliferation and differentiation of tumor cells, thereby affecting the growth and development of tumors (Hu *et al.* 2019; Vistro *et al.* 2019a, b). ECM can influence tumor development by regulating the migration and activation of inflammatory cells. Studies have shown that the composition and structure of ECM can affect the migration and activation capabilities of inflammatory cells, thereby affecting the occurrence and progression of tumors (Li *et al.* 2021; Sun *et al.* 2024a, b). That secondly, inflammation can influence tumor progression by regulating the degradation and reconstruction of the extracellular matrix. The ECM is a non-cellular component of the TME and is mainly composed of collagen I, which has been shown to align with tumor boundaries, thereby promoting the migration of cancer cells (Ray *et al.* 2017). ECM proteins are also considered to be important components of the metastatic niche, maintaining the properties of cancer stem cells and promoting the growth of metastatic cells. Inflammation can activate a variety of proteases and kinases, and tumor ECM induces tumor cell metastasis through extracellular proteases such as matrix metalloproteinases (MMPs), thus affecting tumor metastasis and spread. The immune response caused by inflammation in the TME can secrete a series of cytokines and chemokines to directly regulate the structure and function of the ECM, and can also control the ECM by directly synthesizing ECM components and enzymes that decompose ECM (Vistro *et al.* 2019; Chen *et al.* 2022). At the same time, for tumor cells, ECM is equivalent to a barrier, which can protect cancer from treatment and support tumor progression (Yuan *et al.* 2023). ECM has an important impact on tumor occurrence, proliferation and metastasis, and it can even be said that ECM is a protective A rock-solid barrier to tumor survival and progression; however, without an unbreakable barrier, the ECM can also

serve as a breakthrough for anti-tumor therapies. Therefore, it is important to further study the impact of the interaction of inflammation and tumors in the TME on the ECM to explore how it changes. The molecular composition of the ECM and how to reshape the ECM are very helpful in finding new tumor treatment targets.

Inflammatory factors and TME

Inflammatory factors: Inflammatory factors participate in the inflammatory response in the TME and also have a certain impact on tumors. During inflammation, immune cells and stromal cells synthesize cytokines through intercellular signal transduction to regulate the inflammatory response; however, during chronic inflammation, some cytokines may cause cancer, for example, large amounts are produced in chronically inflammatory tissues. Inflammatory cytokines, some tumor cells can respond to these cytokines some tumor cells are able to respond to these cytokines and gain a growth advantage (Vanni *et al.* 2015). Cytokines play a crucial role in the occurrence and development of chronic inflammation and tumors. In an inflammatory state, the levels of cytokines will increase significantly, causing the proliferation and differentiation of tissue cells and also increasing the risk of cancer disease (Kim *et al.* 2017; Sun *et al.* 2023a, b). In addition, cytokines can also affect the regulation of the immune system, reducing the body's immunity to tumors, thus promoting the growth and spread of tumors (Yu *et al.* 2018). Therefore, to prevent and treat chronic inflammation and tumors, it is necessary to effectively control cytokine levels. Inflammation does not always have a positive effect on tumor cells. In fact, inflammation can also play an anti-tumor role. Immune cells during inflammation can release anti-tumor factors, such as NK cells, which can also secrete cytokines. The interferon-γ and TNF-α they secrete are used to inhibit tumor cell proliferation, tumor angiogenesis and multi-stage carcinogenesis (Fig. 2). The mechanisms by which inflammation affects tumor cells are complex and diverse. Cytokines and chemicals generated during inflammation can bind to receptors on the surface of tumor cells and activate a variety of signaling pathways. For example, TNF-α is an important inflammatory mediator that can activate TNF receptors on the surface of tumor cells. It then activates the NF-KB pathway and MAPK pathway to promote the proliferation, survival and invasion of tumor cells, thereby promoting the development of tumors (Kang *et al.* 2022; Ali *et al.* 2023a, b, c). In addition, inflammation can also change the phenotype of tumor cells, making them more invasive and metastatic. Inflammation can also further promote the growth and spread of tumor cells by changing their metabolic pathways and increasing their demand for nutrients.

TGF-*β* is a multifunctional cytokine belonging to the transforming growth factor superfamily, which plays an important role in physiological activities such as cell proliferation, survival and differentiation (Marquevielle *et al.* 2020). This family includes TGF-*β* subtypes TGF-*β*1, -*β*2 and -*β*3, as well as factors such as growth inhibitory factors, On the other hand, TGF-*β*, an immunosuppressive cytokine, is produced in response to damage to stop inflammation from becoming out of control. TGF-*β* in the tumor microenvironment can help tumor cells proliferate, invade, and disseminate. Tumor-associated TGF-*β* can come from stromal cells, inflammatory cells invading the tumor, or the cancer cells themselves. This cytokine has a cytoplasmic serine/threonine kinase domain and interacts to the II Transforming Growth Factor Beta Receptor Type II (TGFBRII) to mediate its actions (Massagué 2008). Mutations in the TGFBRII gene are frequently seen in malignant tumors with microsatellite instability, which enables cancer cells to evade TGF-*β*'s inhibitory action (Chou *et al.* 2012). TGF-*β* is a key player in malignancies, controlling the process of tumor cells' epithelial to mesenchymal transition (EMT) in addition to suppressing immune responses. Tumor invasion, metastasis, and dissemination are made possible by the increased invasiveness and mobility of tumor cells that result from the start of the EMT process. As a result, TGF-*β* modulation may be crucial in encouraging the growth of tumors. It has been established that the TGF-*β* signaling axis strongly induces the EMT process in hepatocellular cancer (Steinway *et al.* 2014; Huang *et al.* 2018). Cohen *et al.* (2015) demonstrated that EMT may be induced in inflammatory breast cancer by activated human T lymphocytes secreting inflammatory factors such as TNF-*α*, IL-6 and TGF-*β*. Additionally, TGF-*β* is crucial for local invasion. Clinical evidence, however, indicates that it also aids in the promotion of cancers' distant metastases (Dalal *et al.* 1993) observed that TGF-*β* levels were elevated in most metastases of breast invasive ductal carcinoma. Previous studies have shown that TGF-*β* is involved in two processes that are critical to the development of distant metastasis, namely the initiation of tumor cells and the colonization of new tumor metastases. TGF-*β* induces angiopoietin-like 4 in cancer cells and plays an important role in the growth and metastasis of primary breast tumors. It promotes the destruction of intercellular junctions in lung capillaries, increases their permeability, and allows cancer cells to Intrapulmonary dissemination C-reactive protein (CRP) is a biomarker synthesized by liver cells in response to pro-inflammatory cytokines; the liver seems to be the main source of CRP in the blood, as shown by the research of Pierce *et al.* (2009), who showed that systemic CRP and human serum amyloid A protein (SAA) are indicators of chronic inflammation, and that there is a negative relationship between these markers and breast cancer survival; chronic inflammation may therefore raise the chance of breast cancer recurrence. Non-specific acute phase proteins, such as CRP and SAA, are released in reaction to several cytokines, including TNF-α, IL1 and IL-6. When, inflammation or infection occurs, the amount of

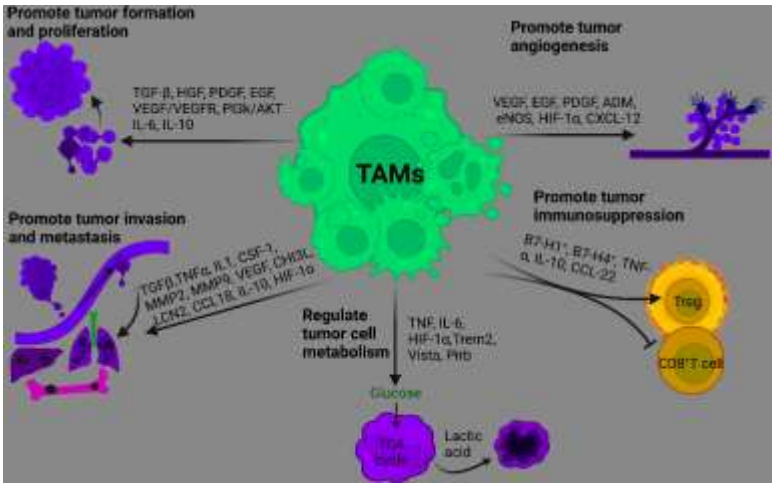

Fig. 2: TAMs facilitate tumor progression by promoting tumor cell proliferation, invasion, migration, angiogenesis, immunosuppression and metabolism

CRP increases significantly, up to 1,000-fold. This increase causes CRP to participate in the activation of the classical complement pathway (Huang *et al.* 2019; Ali *et al.* 2022; Otero *et al.* 2022). CRP appears in the form of a homopentamer, called natural CRP (natural C-reactive protein, nCRP), and can dissociate at the site of inflammation to form monomeric CRP (monomeric C-reactive protein, mCRP). Both CRP isoforms have biological functions. nCRP has anti-inflammatory properties and induces phagocytosis and promotes apoptosis upon activation of complement *via* the classical pathway, in contrast to mCRP, which is a chemotaxis inducer and recruits leukocytes to sites of inflammation. It can also enhance the expression of IL-8 and increase the amount of monocyte chemo attractant protein 1, and induce the production of nitric oxide. The recruitment of inflammatory cells is facilitated by SAA. Elevated CRP and SAA were linked to a worse disease-free survival rate in a research with 734 breast cancer survivors that connected post-treatment inflammatory markers with breast cancer survival (Pierce *et al.* 2009).

Inflammasomes

As a multimeric protein complex, the inflammasomes participate in the inflammatory response and also has a certain impact on the development of tumors. Inflammasomes are involved in every aspect of tumor development and have tumor-promoting and tumor-suppressing functions. Inflammasome plays an important role in the progression of malignant tumors, and its regulatory role is critical to the progression of many tumors. Depending on which inflammasomes are present in a given tumor, inflammasomes can either promote or hinder tumor growth, according to credible study findings that highlight their dual role in the TME (Julienne *et al.* 2019). Malignant tumor incidence, invasion, metastasis, immune evasion, chemotherapy, and radiation are all facilitated by inflammasomes. Notably, some TME cell subsets, including as tumor cells, tumor-associated macrophages, tumor-associated fibroblasts, and myeloid-derived suppressor cells, can activate inflammasomes (Das *et al.* 2020). Furthermore, the inflammasomes can be activated under different conditions, leading to different downstream changes. According to separate research, a material called plasma may start entirely distinct or even opposing processes to control the activation of inflammasomes. For instance, *via* raising reactive oxygen species (ROS) levels, lactate stimulates nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) in macrophages. Lactate simultaneously stimulates the production of TGF-β from tumor cells, which triggers autophagy in macrophages in a de-SMAD-dependent way, clearing ROS and reducing inflammation (Tu *et al.* 2021).

The cancer-promoting effect of prostaglandins in TME

Prostaglandin (PG) also has a certain influence on the occurrence and development of tumors. PG is an active substance, which is composed of unsaturated fatty acids and is synthesized from arachidonic acid through cyclooxygenase (COX). PG is ubiquitous in inflammatory reactions, and its synthesis is significantly increased in inflammatory areas. Therefore, prostaglandins play an important role in inflammation and pain processing and have also been extensively studied for their role in cancer, cardiovascular disease, and neuroscience (Dikalov *et al.* 2022). To better understand their role in various physiological and pathological processes.

Further in-depth research on the functions and regulatory mechanisms of prostaglandins is needed. There are usually two subtypes of COX, namely COX-1 and COX-2. Among them, COX-2 plays an important role in the occurrence and development of cancer. Studies have found

that COX-2 is used in the diagnosis of prostate cancer patients. The expression of COX-2 is higher. Since COX-2 is dose-related to prostate-specific antigen, COX-2 detection is expected to become a biomarker for the diagnosis and prognosis of prostate cancer patients. COX-2 can induce colon cancer cells to produce antigenic factors, which may contribute to the growth of new blood vessels and stimulate tumor growth (Tsujimoto *et al.* 2016; Gandahi *et al.* 2020). The stimulatory effect of COX-2 is not limited to colon cancer, as increased expression of this gene has also been observed in lungs, prostate, and breast cancers. Prostaglandins are also related to ROS and reactive nitrogen species (RNS). Peroxynitrite is a highly reactive product of the reaction between nitric oxide and superoxide and is a short-lived oxidant. Also, a potent inducer of cell death it can stimulate the production of COX-2. Animal models and epidemiological observations suggest that treatment with NSAIDs reduces the risk of gastrointestinal cancer, particularly in the treatment of colorectal cancer. COX-2 specific inhibitors show a more obvious ability to inhibit colon cancer than traditional non-steroidal anti-inflammatory drugs, but the mechanism between COX-2 expression and colorectal cancer is unclear (Goodwin *et al.* 1999); there are currently studies It is believed that COX-2 plays an important role in the secretion of prostaglandin E2, which interacts with EP receptors. The E-series of prostaglandin receptors type 2 (EP2) is considered a tumor promoter mouse with EP2 receptor knockout develop lung, skin, and breast tumors after induction of carcinogenesis. The risk is significantly reduced. EP2 mainly promotes carcinogenesis by activating vascular endothelial growth factor to induce related angiogenesis. On the other hand, it also governs the motility and survival of endothelial cells, which in turn governs angiogenesis (Chang *et al.* 2005). Another receptor linked to the development of tumors is prostaglandin receptor 4. The activation of prostaglandin receptor 4 by PGE2 results in the formation of an immunological response that is tumorigenic.

Oxidative stress caused by inflammation

There is a close relationship between inflammation, oxidative stress and tumorigenesis. Oxidative stress has the ability to regulate inflammation, and inflammation causes damage through oxidative stress (Haseeb *et al.* 2019a, b; Wang *et al.* 2020). One of the mechanisms by which inflammation induces carcinogenesis involves the generation of ROS and RNS. Various inflammatory cells, such as activated neutrophils and macrophages, can generate ROS and RNS by activating a variety of oxidases, including reduced nicotinamide adenine dinucleotide phosphate oxidase and xanthine oxidase, inducible nitric oxide synthase and myeloperoxidase, *etc*. Various types of inflammatory cells, such as activated neutrophils and macrophages, can activate reduced nicotinamide adenine dinucleotide phosphate oxidase, xanthine oxidase, inducible nitric oxide synthase, and Oxidants such as myeloperoxidase generate ROS and RNS. Initially, when bacteria and parasites invade the human body, they will activate the human immune system, cause an inflammatory response, and generate oxidants such as ROS and RNS.

These oxidants are produced to kill bacteria and parasites, but they cause damage to nucleic acids, proteins, and lipids, frequently with the induction of DNA damage leading to mutations and further neoplastic transformation. The oxidants synthesized in the above process can induce gene mutations. For example, the generation of ROS can lead to the above changes. 8-oxo-dG is a very important biomarker of oxidative DNA damage. It exists both in intact DNA and in free products formed during the repair process (Xiao *et al.* 2021). 8-oxo-dG can cause G:C to A:T transversion in cancer (Nguyen *et al.* 2020), causing DNA damage; The same RNS also induces mutations in the gene for which nitric oxide is synthesized by nitric oxide synthase. During inflammation, many inflammatory cells, especially macrophages and neutrophils, induce iNOS expression in the presence of bacterial products. Oxynitrite is the product of the diffusion-controlled reaction between nitric oxide and superoxide radicals (Cao *et al.* 2018). Compared with nitric oxide, it is more unstable and therefore causes greater damage to DNA. Peroxynitrite causes the production of 8-oxodG, leading to the conversion of nucleic acid bases and the occurrence of translocation production, thus causing gene mutations. Studies have found that nitric oxide is also related to the occurrence of gastric cancer, and Helicobacter pylori infection is one of the main factors in the occurrence of gastric cancer. Helicobacter pylori activates inflammatory genes in the gastric epithelium, leading to increased expression of nitric oxide synthase through activation of related pathways (Cai *et al.* 2024; Wang *et al.* 2024).

Inflammation-related non-coding RNA and TME

Long non-coding RNA and TME: Long noncoding RNA (lncRNA) is a distinct kind of RNA molecule with a length of more than 200 nucleotides, which is closely related to biological processes such as transcription regulation, chromatin remodeling and signal transduction. Research shows that lncRNA plays an important role in regulating the occurrence and development of tumors. This discovery provides new ideas and potential targets for further understanding of the pathogenesis of cancer and the development of new treatment strategies, epigenetically induced MYC interactions. The lncRNA 1 (epigenetically induced MYC interacting lncRNA 1 Gene, EPIC1) gene was first identified as an oncogene in luminal B breast cancer, and studies also found that EPIC1 was found to be highly expressed in prostate cancer and lung cancer (Wang *et al.* 2018). Research in recent years has shown that lncRNA plays a crucial regulatory role in the occurrence and development of tumors. They can regulate the

expression of genes and the activity of signaling pathways by interacting with DNA, RNA and proteins in the TME, therefore, it will affect the reproduction, invasion, spread and drug resistance of tumor cells. Some lncRNAs bridge the link between inflammation and tumors in the TME. For example, H19 is a type of lncRNA, and studies have shown that in some cancers, the expression level of H19 increases significantly and is involved in the invasion of tumor cells; in addition, H19 can target and regulate TGF-β1 in prostate cancer cells (Matouk *et al.* 2014; Tunio *et al.* 2024). This indicates that H19 plays an essential role in the regulation of inflammation. According to increasing evidence, H19 plays a vital role in tumor proliferation and differentiation. In addition, it is also involved in EMT and the process of mesenchymal cell epithelial cell transformation, which indicates that it plays a significant role in tumor proliferation and differentiation. Contributions are made during the occurrence and development process. Studies have found that lncRNA DANCR affects many types of cancer and is overexpressed in most cancers (Lu *et al.* 2018; Chen *et al.* 2024). Recently, Zhang *et al.*(2020) found that lncRNA DANCR is an important factor in inflammation and inflammation-mediated EMT and cancer stemness. The master regulator, lncRNA DANCR, not only maintains these phenotypes in advanced triple-negative breast cancer, but can also fully induce these phenotypes in normal breast epithelial cells or early breast cancer cells. ZFAS1 is a gene that is found in several cancers including hepatocellular carcinoma, colorectal cancer, gastric cancer, ovarian cancer, glioma, osteosarcoma, esophageal squamous cell carcinoma, acute myeloid leukemia, non-small cell lung cancer, breast cancer *etc*. There are abnormally expressed lncRNAs (Zhou *et al.* 2016) and up-regulation of ZFAS1 expression is positively connected with lymph node metastasis of colorectal cancer, gastric cancer, ovarian cancer and non-small cell lung cancer (He *et al.* 2019); ZFAS1 can regulate miR-588 and regulate the body's inflammatory response through the miR-588/ROCK1 axis (Geng *et al.* 2022) and miR-588 has been reported to be involved in the pathogenesis of lung cancer, human breast cancer, colorectal cancer and other tumors (Yu *et al.* 2017; Fattahi *et al.* 2019; Dahiri *et al.* 2022); therefore, ZFAS1 can regulate inflammatory responses and is abnormally expressed in many tumors, further exploring its mechanism of action will help discover the role of lncRNA in tumor occurrence and development.

In the TME, lncRNA plays its role mainly in the pre-transcriptional, during-transcriptional and post-transcriptional stages. lncRNA can affect biological behaviors such as tumor cell proliferation, invasion and metastasis by regulating the expression of tumor-related genes. At the same time, some lncRNA it can affect the occurrence and development of tumors by regulating inflammatory responses. Some inflammation-related lncRNAs have also been found to be abnormally expressed in tumor tissues and are related to tumor immune evasion and drug resistance, because lncRNAs in the TME play an important role in tumor occurrence and development. It has an important impact on proliferation. Some lncRNA-based drugs have entered the clinical trial stage and have shown good tumor treatment effects. For example, mtlncRNA has been approved for clinical trials by the US Food and Drug Administration. mtlncRNA is a newly discovered gene in mitochondria. Encoded lncRNA, like lncRNA produced in the nucleus, mtlncRNA also participates in a variety of biological processes by regulating the permeability of the mitochondrial membrane, which can induce cell cycle disorders and ultimately lead to cell death (Shuo *et al.* 2023; Zou *et al.* 2024). Therefore, compared with traditional drug targets, gene therapy targeting lncRNA is still an emerging concept. Clinical trials that have been conducted have shown that lncRNA has great potential in tumor treatment. Continue to conduct in-depth research and development of lncRNA-related drugs can provide new strategies for tumor treatment.

MicroRNA and TME

miRNA is a type of non-coding RNA molecule consisting of approximately 22 nucleotides. They perform a vital role in regulating gene expression and cell function. Although the biosynthesis of miRNA is tightly regulated, in cancer cells, an imbalance in the regulation of miRNA can be observed due to changes in biosynthetic pathway proteins (Ma *et al.* 2007; Merritt *et al.* 2008). In addition to the effects of changes within cancer cells on miRNA, the tumor microenvironment can also directly affect the levels of miRNA. These changes may be due to biosynthetic defects caused by hypoxia or changes in miRNA transcription result (Ma Weinberg 2007; Rupaimoole *et al.* 2014). Although biosynthetic defects lead to decreased miRNA levels, many oncogenic miRNAs are significantly increased in cancer. The mechanisms by which oncogenic miRNA expression increases in cancer are diverse and complex; research by Chen *et al.* (2024) found that miRNAs contained in exosomes can regulate tumor immunity and microenvironment, and may promote tumor invasion, metastasis, and angiogenesis. Some miRNAs can regulate the link between inflammation and tumors. miR-146a is a type of miRNA that is highly expressed in inflammatory responses; it regulates the expression of multiple target genes and helps regulate the secretion of inflammatory cytokines (Taganov *et al.* 2006; Liang *et al.* 2019). The function of inflammatory miR-146a mainly works by inhibiting the activation of inflammatory signaling pathways. Abnormal expression of miR-146a is related to the occurrence and progression of various cancers. For example, the expression quantity of miR-146a is down-regulated in breast cancer, hormone-refractory prostate cancer, and pancreatic cancer; in addition, in tumors, the activation of the inflammatory response can enhance the invasive ability of tumor cells, thereby leading to tumor

metastasis and spread. The research results of (Li *et al.* 2010; Mangi *et al.* 2015; Bai *et al.* 2019) found that the expression of miR-146a is often suppressed in the early stages of cancer progression, while overexpression of inflammatory miR-146a can significantly inhibit the invasion and metastasis ability of tumor cells and reduce the risk of tumor metastasis.

Studies have found that miRNAs are also involved in regulating TAMs to affect tumor progression. TAMs generally consist of two phenotypes, M1 macrophages are mainly involved in inflammatory responses and anti-tumor immunity, while M2 macrophages usually exhibit anti-inflammatory and pro-tumor effects. miRNA affects TAM polarization. In colorectal cancer, extracellular vesicles released by cancer cells containing miR-145 can polarize macrophages to an M2 phenotype, thereby promoting tumor progression (Shinohara *et al.* 2017; Khan *et al.* 2016, 2019). In similar studies on EMT-mediated TAM activation, the EMT transcription factor Snai1 plays a significant role in tumors and can activate miR-21, thereby causing tumor cells to release exosomes containing miR21. These exosomes are taken up by $CD14^+$ human monocytes, hinder the expression of M1 markers, increase the expression of M2 markers, and ultimately accelerate tumor progression. In addition, studies have found that colon cancer cells containing human mutant p53 can reprogram macrophages under tumor-supportive and anti-inflammatory conditions. MiR1246-enriched exosomes, in which human mutant p53 is one of its major components, can be released from colon cancer cells and taken up by macrophages, which exhibit a miR-1246-dependent manner.

miRNAs are expressed differently in immune cells involved in different inflammatory responses and can control the body's inflammatory response in various methods through directing the expression of key indication transduction molecules in inflammation. At the same time, as mentioned above, miRNA also affects the development, metastasis and drug resistance of tumors by regulating the expression of oncogenes and tumor suppressor genes; the important role of miRNA in inflammation and tumors makes miRNA a potential target for the treatment of tumors. Point, current miRNA treatment strategies include miRNA mimics and miRNA antagonists, and miRNA has unique advantages. The effect of miRNA is highly specific and selective, which can reduce the impact on non-target genes, and miRNA mimics and miRNA Antagonists can be delivered targeted through carriers such as nanoparticles, thereby improving therapeutic effects and reducing side effects. In addition, miRNA has high specificity and sensitivity in tumors and is a qualified biomarker that can be used to monitor tumors, occurrence and prognosis of cancer. In summary, miRNA has great potential in tumor treatment and monitoring. Continued in-depth research on miRNA is expected to discover new miRNA biomarkers and new tumors in future tumor treatment strategies.

Conclusion

TME is an important component of tumor growth and progression. It is a highly complex local environment in which tumors grow, and tumor cells have extremely strong adaptability and can quickly adapt to treatment and environmental changes. Therefore, tumors and inflammation play a vital role in TME. The specific mechanisms of interactions between them need to be studied in depth to further discover the connections between them. The mechanism of tumor genesis and clinical treatment has been an enduring topic; research has found that controlling inflammation can hypothetically change the dynamics of tumor development and can be used to design new treatment options for the treatment of different cancers while improving the efficacy of traditional anti-cancer treatments. Huang *et al.* (2021) and Zhang *et al.* (2024) found that oseltamivir, a drug used to treat influenza viruses, had differential effects on inducing liver cancer cell death *in vitro* and *in vivo* and suggested the use of non-tumor drugs as an alternative method for liver cancer treatment. Therefore, traditional tumor treatment and anti-inflammatory treatment can be combined to exert a synergistic effect in tumor treatment; in addition, emerging targeted microenvironment treatments have also gained widespread recognition. By in-depth understanding of the characteristics of the TME and targeting the TME can bring new breakthroughs in tumor treatment. Emerging treatments for pancreatic ductal adenocarcinoma have begun to use treatment strategies targeting the TME. Finally, according to the different roles of different tumors in the TME, Different characteristics, collaborative treatment of stromal cells in multiple microenvironments and the continuous discovery of new target markers may be future research directions.

Acknowledgements

We would like to express our gratitude to Dean, Faculty of Animal Husbandry and Veterinary Sciences, Sindh Agriculture University for his support throughout this research.

Author Contribution

S. Tunio: conceptualization, data curation, investigations, visualization, writing and editing the original draft; PK Sial and H Tunio: conceptualization, visualization, writing and editing the original draft; MK Menghwar: analysis, writing; M Meena – analysis, review and editing; MA Memon: conceptualization, analysis, supervision.

Conflicts of Interest

This work contains no potential conflicts of interest.

Data Availability

No data was used for the research described in the article

Ethics Approval

This is a review article therefore, there is no need of ethical approval.

Funding Source

Funding is not available for this work.

References

Ahmed N, P Yang, H Chen, IA Ujjan, A Haseeb, L Wang, F Soomro, S Faraz, B Sahito, W Ali (2018). Characterization of inter-Sertoli cell tight and gap junctions in the testis of turtle: Protect the developing germ cells from an immune response. *Microb Pathog* 123:60–67

Ali W, Y Chen, JA Gandahi, IH Qazi, J Sun, T Wang, Z Liu, H Zou (2023a). Cross-Talk between selenium nanoparticles and cancer treatment through autophagy. *Biol Trace Element Res* 202:2931–2940

Ali W, K Deng, Y Bian, Z Liu, H Zou (2023b). Spectacular role of epididymis and bio-active cargo of nano-scale exosome in sperm maturation: A review. *Biomed Pharmacother* 164:114889

Ali W, MA Memon, AS Khoso, S Tunio, A Ayoob, MB Arain, M Hussain (2023c). Biological characteristics and immunological role of mesenchymal stem cells for improvement of health. *Intl J Agric Biol* 30:51–57

Ali W, Y Ma, J Zhu, H Zou, Z Liu (2022). Mechanisms of cadmium-induced testicular injury: A risk to male fertility. *Cells* 11:3601

Arbab S, R Buriro, SU Bhugio, AH Shah, J Soomro, SA Fazilani, WA Vistro (2020). Antimicrobial properties of aloe vera gel extracts against bacterial isolates from wound of donkey. *Pak J Zool* 52:2333–2340

Ayoob MF, ZA Nizamani, AA Kamboh, M Ayoob, WA Vistro, AS Baloch (2021). Pathology of induced Velogenic Viscerotropic Newcastle Disease (VVND) in Japanese Quail and Myna. *Pak J Zool* 53:521–527

Azhar M, JA Gadahi, B Bhutto, S Tunio, WA Vistro, H Tunio, S Bhutto, T Ram (2023). Babesiosis: Current status and future perspectives in Pakistan and chemotherapy used in livestock and pet animals. *Heliyon* 9:e17172

Bai X, Y Shi, I Tarique, WA Vistro, Y Huang, H Chen, A Haseeb, NS Gandahi, P Yang, Q Chen (2019). Multivesicular bodies containing exosomes in immune-related cells of the intestine in zebrafish (Danio rerio): Ultrastructural evidence. *Fish Shellfish Immunol* 95:644–649

Banchereau J, F Briere, C Caux, J Davoust, S Lebecque, Y Liu, B Pulendran, K Palucka (2000). Immunobiology of dendritic cells. *Annu Rev Immunol* 18:767–811

Briukhovetska D, J Dörr, S Endres, P Libby, CA Dinarello, S Kobold (2021). Interleukins in cancer: From biology to therapy. *Nat Rev Cancer* 21:481–499

Cai F, X Yang, G Ma, P Wang, M Zhang, N Zhang, R Zhang, H Liang, Y Nie, C Dong (2024). EGLN3 attenuates gastric cancer cell malignant characteristics by inhibiting JMJD8/NF-κB signalling activation independent of hydroxylase activity. *Brit J Cancer* 130:1–16

Cao J, W An, AG Reeves, AR Lippert (2018). A chemiluminescent probe for cellular peroxynitrite using a self-immolative oxidative decarbonylation reaction. *Chem Sci* 9:2552–2558

Chang SH, CH Liu, MT Wu, T Hla (2005). Regulation of vascular endothelial cell growth factor expression in mouse mammary tumor cells by the EP2 subtype of the prostaglandin E2 receptor. *Prostagl Lipid Mediators* 76:48–58

Chen XM, YY Liu, BY Tao, XM Xue, XX Zhang, LL Wang, H Zhong, J Zhang, SM Yang, QP Jiang (2022). NT5E upregulation in head and neck squamous cell carcinoma: A novel biomarker on cancer-associated fibroblasts for predicting immunosuppressive tumor microenvironment. *Front Immunol* 13:975847

Chen Y, H Jin, W Ali, T Zhuang, J Sun, T Wang, J Song, Y Ma, Y Yuan, J Bian, Z Liu, H Zou (2024). Co-exposure of polyvinyl chloride microplastics with cadmium promotes nonalcoholic fatty liver disease in female ducks through oxidative stress and glycolipid accumulation. *Poult Sci* 103:104152

Choi J, W Choi, Y Joo, H Chung, D Kim, SJ Oh, SH Kim (2021). FGF2-primed 3D spheroids producing IL-8 promote therapeutic angiogenesis in murine hindlimb ischemia. *NPJ Regener Med* 6:48

Chou YT, CH Hsieh, SH Chiou, CF Hsu, YR Kao, CC Lee, CH Chung, YH Wang, HS Hsu, ST Pang (2012). CITED2 functions as a molecular switch of cytokine-induced proliferation and quiescence. *Cell Death Different* 19:2015–2028

Cohen EN, H Gao, S Anfossi, M Mego, NG Reddy, B Debeb, A Giordano, S Tin, Q Wu, RJ Garza, M Cristofanilli, SA Mani, DA Croix, NT Ueno, WA Woodward, R Luthra, S Krishnamurthy, JM Reuben (2015). Inflammation mediated metastasis: Immune induced epithelial-to-mesenchymal transition in inflammatory breast cancer cells. *PloS One* 10:e0132710

Dahiri GN, AA Memon, Q Kalwar, A Kaka, WA Vistro, YM Jalbani, K Nazish, JP Kolhi (2022). Improvement of Fertility Rate Using Ovsynch and Biostimulation Protocols with Timed Artificial Insemination in Thari Cattle. *Pak J Zool* 54:2981–2984

Dalal BI, PA Keown, AH Greenberg (1993). Immunocytochemical localization of secreted transforming growth factor-beta 1 to the advancing edges of primary tumors and to lymph node metastases of human mammary carcinoma. *Amer J Pathol* 143:381–389

Das S, B Shapiro, EA Vucic, S Vogt, D Bar-Sagi (2020). Tumor cell–derived IL1β promotes desmoplasia and immune suppression in pancreatic cancer. *Cancer Res* 80:1088–10100

Davidson S, M Coles, T Thomas, G Kollias, B Ludewig, S Turley, M Brenner, CD Buckley (2021). Fibroblasts as immune regulators in infection, inflammation and cancer. *Nat Rev Immunol* 21:704–717

Dikalov SI, AE Dikalova, IA Kirilyuk (2022). Coupling of phagocytic NADPH oxidase activity and mitochondrial superoxide production. *Front Cardiovasc Med* 9:942736

Duan Y, Y Zhang, T Wang, J Sun, W Ali, Y Ma, Y Yuan, J Gu, J Bian, Z Liu (2023a). Interactive mechanism between connexin43 and Cd-induced autophagic flux blockage and gap junctional intercellular communication dysfunction in rat hepatocytes. *Heliyon* 9:e21052

Duan Y, Y Zhao, T Wang, J Sun, W Ali, Y Ma, Y Yuan, J Gu, J Bian, Z Liu, H Zou (2023b). Taurine alleviates cadmium-induced hepatotoxicity by regulating autophagy flux. *Intl J Mol Sci* 24:1205

Fattahi F, J Kiani, M Khosravi, S Vafaei, A Mohammadi, Z Madjd, M Najafi (2019). Enrichment of up-regulated and down-regulated gene clusters using gene ontology, miRNAs and lncRNAs in colorectal cancer. *Combin Chem High Throughput Screen* 22:534–545

Finn OJ (2018). A believer's overview of cancer immunosurveillance and immunotherapy. *J Immunol* 200:385–391

Gandahi NS, B Ding, Y Shi, X Bai, JA Gandahi, WA Vistro, Q Chen, P Yang (2020). Identification of telocytes in the pancreas of Turtles—A role in cellular communication. *Intl J Mol Sci* 21:2057

Geng Z, B Dong, W Lv, Z Wang, X Wang, Y Huang, Y Wang, L Xu (2022). LncRNA ZFAS1 regulates the proliferation, oxidative stress, fibrosis, and inflammation of high glucose-induced human mesangial cells *via* the miR-588/ROCK1 axis. *Diabetol Metab Syndrome* 14:21

Goodwin DC, ML Lisa, LJ Marnett (1999). Effects of nitric oxide and nitric oxide-derived species on prostaglandin endoperoxide synthase and prostaglandin biosynthesis. *FASEB J* 13:1121–1136

Greten FR, SI Grivennikov (2019). Inflammation and cancer: Triggers, mechanisms, and consequences. *Immunity* 51:27–41

Hanahan D, RA Weinberg (2011). Hallmarks of cancer: The next generation. *Cell* 144:646–674

Haseeb A, I Tarique, X Bai, P Yang, WA Vistro, Y Huang, SA Fazllani, Z Ahmed, Q Chen (2019a). Inhibition of autophagy impairs acrosome and mitochondrial crista formation during spermiogenesis in turtle: Ultrastructural evidence. *Micron* 121:84–89

Haseeb A, I Tarique, A Iqbal, NS Gandahi, X Bai, Y Liang, Y Huang, H Chen, Q Chen, P Yang (2019b). Characterization of multilamellar bodies and telocytes within the testicular interstitium of naked mole rat Heterocephalus glabe. *Theriogenology* 138:111–120

He A, S He, X Li, L Zhou (2019). ZFAS 1: A novel vital oncogenic lnc RNA in multiple human cancers. *Cell Prolifer* 52:1-9

Hu F, W Zeng, X Liu (2019). A gene signature of survival prediction for kidney renal cell carcinoma by multi-omic data analysis. *Intl J Mol Sci* 20:5720

Huang PJ, C Chiu, M Hsiao, J Yow, B Tzang, T Hsu (2021). Potential of antiviral drug oseltamivir for the treatment of liver cancer. *Intl J Oncol* 59:109

Huang Y, H Chen, P Yang, X Bai, Y Shi, WA Vistro, I Tarique, A Haseeb, Q Chen (2019). Hepatic lipid droplet breakdown through lipolysis during hibernation in Chinese Soft-shelled turtle (*Pelodiscus sinensis*). *Aging* 11:1990

Huang Y, P Yang, H Chen, X Bai, X Wang, WA Vistro, A Haseeb, Y Shi, Q Chen (2018). A Lamellar structure contributes to autophagosome biogenesis and mitophagy in zebrafish hepatocytes. *Fish Shellfish Immunol* 81:83–91

Jiang X, J Wang, X Deng, F Xiong, J Ge, B Xiang, X Wu, J Ma, M Zhou, X Li (2019). Role of the tumor microenvironment in PD-L1/PD-1-mediated tumor immune escape. *Mol Cancer* 18:10

Jones WD, CM Michener, C Biscotti, I Braicu, J Sehouli, MK Ganapathi, RN Ganapathi (2020). RNA immune signatures from pan-cancer analysis are prognostic for high-grade serous ovarian cancer and other female cancers. *Cancers* 12:620

Joshi RS, SS Kanugula, S Sudhir, MP Pereira, S Jain, MK Aghi (2021). The role of cancer-associated fibroblasts in tumor progression. *Cancers* 13:1399

Julienn F, N Delorme, F Lagarde (2019). From macroplastics to microplastics: Role of water in the fragmentation of polyethylene. *Chemosphere* 236:124409

Kang X, Y Chen, X Xin, M Liu, Y Ma, Y Ren, J Ji, Q Yu, L Qu, S Wang, G Liu, C Xiang, L Yang (2022). Human amniotic epithelial cells and their derived exosomes protect against cisplatin-induced acute kidney injury without compromising its antitumor activity in mice. *Front Cell Dev Biol* 9:752053

Khan SA, IB Kalhoro, JA Gandahi, WA Vistro, Q Kalwer, I Ali, TA Khokhar, MH Mangi (2019). Puberty associated micro anatomical modification in testes and epididymis of Teddy goat (*Capra hircus*). *Pure Appl Biol* 8:1281–1286

Khan SA, BI Kalhoro, JA Gandahi, AN Tunio, WA Vistro, M Ahmed, SK Fareed (2016). Gross anatomical studies on testis and epididymis at pre-pubertal and pubertal stages of Teddy goat. *Acad Res Intl* 7:51–57

Kim H, N Banerjee, RC Barnes, CM Pfent, ST Talcott, RH Dashwood, SU Mertens-Talcott (2017). Mango polyphenolics reduce inflammation in intestinal colitis—involvement of the miR-126/PI3K/AKT/mTOR axis *in vitro* and *in vivo*. *Mol Carcinogen* 56:197–207

Liang Y, S Wang, T An, I Tarique, WA Vistro, Y Liu, Z Wang, H Zhang, Y Shi, A Haseeb (2019). Telocytes as a novel structural component in the muscle layers of the goat rumen. *Cell Transplant* 28:955–966

Li H, G Liu, X Wang, M Li, Z Li, Y Xie, Y Guo (2021). Identification of hub lncRNAs along with lncRNA-miRNA-mRNA network for effective diagnosis and prognosis of papillary thyroid cancer. *Front Pharmacol* 12:748867

Li Y, TG VandenBoom, Z Wang, D Kong, S Ali, PA Philip, FH Sarkar (2010). miR-146a suppresses invasion of pancreatic cancer cells. *Cancer Res* 70:1486–1495

Lin, CC, JH Chiang, CI Li, TF Hsieh, CS Liu, WY Lin, YD Lee, TC Li (2014). Independent and joint effect of type 2 diabetes and gastric and hepatobiliary diseases on risk of pancreatic cancer risk: 10-year follow-up of population-based cohort. *Brit J Cancer* 111:2180–2186

Lochi GM, MG Shah, JA Gandahi, JA Gadahi, SA Hadi, T Farooq, WA Vistro, MM Rahmani (2023). Effect of selenium nanoparticles and chitosan on production performance and antioxidant integrity of heat-stressed broiler. *Biol Trace Elem Res* 201:1977–1986

Lu Y, Z Hu, LS Mangala, ZE Stine, X Hu, D Jiang, Y Xiang, Y Zhang, S Pradeep, C Rodriguez-Aguayo (2018). MYC targeted long noncoding RNA DANCR promotes cancer in part by reducing p21 levels. *Cancer Res* 78:64–74

Ma Li, J Teruya-Feldstein, RA Weinberg (2007). Tumour invasion and metastasis initiated by microRNA-10b in breast cancer. *Nature* 449:682–688

Malyar RM, J Tanha, Z Ziauddin, KS Ismail, M Ibrahimi, AR Khalid, B Hanifullah, SA Haq Banuree, WA Vistro (2021). Amelioration of heat stress-induced hepatic injury in wistar rats by zinc-enriched probiotics: Role of hepatic antioxidant status and serum enzymes activity. *Pure Appl Biol* 10:1494–1503

Mangi MH, AA Kamboh, R Rind, P Dewani, ZA Nizamani, AR Mangi, AR Nizamani, WA Vistro (2015). Seroprevalence of brucellosis in Holstein-Friesian and indigenous cattle breeds of Sindh Province. *Pak J Anim Health Prod* 3:82–87

Marquevielle J, C Robert, O Lagrabette, M Wahid, A Bourdoncle, L Xodo, J Mergny, GF Salgado (2020). Structure of two G-quadruplexes in equilibrium in the KRAS promoter. *Nucl Acids Res* 48:9336–9345

Massagué J (2008). TGFβ in cancer. *Cell* 134:215–230

Matouk IJ, E Raveh, R Abu-lail, S Mezan, M Gilon, E Gershtain, T Birman, J Gallula, T Schneider, M Barkali (2014). Oncofetal H19 RNA promotes tumor metastasis. *Biochim Biophys Acta: Mol Cell Res* 1843:1414–1426

Memon IA, MA Raza, WA Vistro, MF Leghari, AW Nizamani, NA Lail, T Farooq, L Ahmad (2016). Marker assisted molecular investigation of kappa-casein gene in Bos indicus Sindhi genetic group using HINFI restriction enzyme. *Intl Arch BioMed Clin Res* 2:34–39

Merritt WM, YG Lin, LY Han, AA Kamat, WA Spannuth, R Schmandt, D Urbauer, LA Pennacchio, JF Cheng, AM Nick (2008). Dicer, Drosha, and outcomes in patients with ovarian cancer. *New Engl J Med* 359:2641–2650

Mroue R, MJ Bissell (2013). Three-dimensional cultures of mouse mammary epithelial cells. In: *Epithelial Cell Culture Protocols*, 2nd edn., pp:221–250. Randell SH, ML Fulcher (Eds.). Humana Press, Totowa, New Jersey, USA

Nguyen DT, B Wu, H Long, N Zhang, C Patterson, S Simpson, K Morris, WK Thomas, M Lynch, W Hao (2020). Variable spontaneous mutation and loss of heterozygosity among heterozygous genomes in yeast. *Mol Biol Evol* 37:3118–3130

Ning R, Y Pei, Y Sun, X Guo (2021). Carbon ion radiotherapy evokes a metabolic reprogramming and individualized response in prostate cancer. *Front Public Health* 9:777160

Öhlund D, A Handly-Santana, G Biffi, E Elyada, AS Almeida, M Ponz-Sarvise, V Corbo, TE Oni, SA Hearn, EJ Lee (2017). Distinct populations of inflammatory fibroblasts and myofibroblasts in pancreatic cancer. *J Exp Med* 214:579–596

Onuma K, Y Kanda, SS Ikeda, R Sakaki, T Nonomura, M Kobayashi, M Osaki, M Shikanai, H Kobayashi, F Okada (2015). Fermented brown rice and rice bran with *Aspergillus oryzae* (FBRA) prevents inflammation-related carcinogenesis in mice, through inhibition of inflammatory cell infiltration. *Nutrients* 7:10237

Otero R, A Solier-López, V Sánchez-López, J Oto, E Arellano, S Marín, L Jara-Palomares, T Elías, MI Asencio, I Blasco-Esquivias, MRDL Borbolla, JM Sanchez-Diaz, M Real-Dominguez, E Garcia-Cabrera, FJ Rodriguez-Martorell, P Medina (2022). Biomarkers of venous thromboembolism recurrence after discontinuation of low molecular weight heparin treatment for cancer-associated thrombosis (HISPALIS-Study). *Cancers* 14:2771

Palmer AJR, CP Brown, EG McNally, AJ Price, I Tracey, P Jezzard, A Carr, S Glyn-Jones (2013). Non-invasive imaging of cartilage in early osteoarthritis. *Bone Joint J* 95:738–746

Pierce BL, R Ballard-Barbash, L Bernstein, RN Baumgartner, ML Neuhouser, MH Wener, KB Baumgartner, FD Gilliland, BE Sorensen, A McTiernan (2009). Elevated biomarkers of inflammation are associated with reduced survival among breast cancer patients. *J Clin Oncol* 27:3437-3444

Piotrowski I, K Kulcenty, W Suchorska (2020). Interplay between inflammation and cancer. *Rep Pract Oncol Radiother* 25:422–427

Qeadan Fares, P Bansal, JA Hanson, EJ Beswick (2020). The MK2 pathway is linked to G-CSF, cytokine production and metastasis in gastric cancer: A novel intercorrelation analysis approach. *J Transl Med* 18:137

Ran D, D Zhou, G Liu, Y Ma, W Ali, R Yu, Q Wang, H Zhao, J Zhu, Hui Zou (2023). Reactive oxygen species control osteoblast apoptosis through SIRT1/PGC-1α/P53Lys382 signaling, mediating the onset of Cd-induced osteoporosis. *J Agric Food Chem* 71:5991–6002

Ray A, ZM Slama, RK Morford, SA Madden, PP Provenzano (2017). Enhanced directional migration of cancer stem cells in 3D aligned collagen matrices. *Biophys J* 112:1023–1036

Rupaimoole R, SY Wu, S Pradeep, C Ivan, CV Pecot, KM Gharpure, AS Nagaraja, GN Armaiz-Pena, M McGuire, B Zand, HJ Dalton , Justyna Filant , JB Miller , Chunhua Lu , NC Sadaoui, LS Mangala, Morgan Taylor , TVD Beucken, Elizabeth Koch, Cristian Rodriguez-Aguayo, Li Huang, Menashe Bar-Eli, BG Wouters, Milan Radovich, Mircea Ivan, GA Calin, Wei Zhang, Gabriel Lopez-Berestein, AK Sood (2014). Hypoxia-mediated downregulation of miRNA biogenesis promotes tumour progression. *Nat Commun* 5:5202

Shi Q, S Han, X Liu, S Wang, H Ma (2022). Integrated single-cell and transcriptome sequencing analyses determines a chromatin regulator-based signature for evaluating prognosis in lung adenocarcinoma. *Front Oncol* 12:1031728

Shi Y, WA Vistro, X Bai, R Wu, C Chen, Y Huang, SA Fazlani, I Tarique, P Yang, Q Chen (2020). Effect of seasonal variance on intestinal epithelial barriers and the associated innate immune response of the small intestine of the Chinese soft-shelled turtles. *Fish Shellfish Immunol* 97:173–181

Shima T, M Shimoda, T Shigenobu, T Ohtsuka, T Nishimura, K Emoto, Y Hayashi, T Iwasaki, T Abe, H Asamura (2020). Infiltration of tumor-associated macrophages is involved in tumor programmed death-ligand 1 expression in early lung adenocarcinoma. *Cancer Sci* 111:727–738

Shinohara H, Y Kuranaga, M Kumazaki, N Sugito, Y Yoshikawa, T Takai, K Taniguchi, Y Ito, Y Akao (2017). Regulated polarization of tumor-associated macrophages by mir-145 *via* colorectal cancer–derived extracellular vesicles. *J Immunol* 199:1505–1515

Shuo H, X Chen, L Huang (2023). The tumor therapeutic potential of long non-coding RNA delivery and targeting. *Acta Pharm Sin B* 13:1371–1382

Spary LK, J Salimu, JP Webber, A Clayton, MD Mason, Z Tabi (2014). Tumor stroma-derived factors skew monocyte to dendritic cell differentiation toward a suppressive CD14+ PD-L1+ phenotype in prostate cancer. *Oncoimmunology* 3:e955331

Steinway SN, JGT Zañudo, W Ding, CB Rountree, DJ Feith, TP Loughran Jr, R Albert (2014). Network modeling of TGFβ signaling in hepatocellular carcinoma epithelial-to-mesenchymal transition reveals joint sonic hedgehog and Wnt pathway activation. *Cancer Res* 74:5963–5977

Sun J, Y Chen, T Wang, W Ali, Y Ma, Z Liu, H Zou (2024a). Role of mitochondrial reactive oxygen species-mediated chaperone-mediated autophagy and lipophagy in baicalin and n-acetylcysteine mitigation of cadmium-induced lipid accumulation in liver. *Antioxidants* 13:115

Sun J, L Yan, Y Chen, T Wang, W Ali, Y Ma, Y Yuan, J Gu, J Bian, Z Liu (2024b). TFAM-mediated intercellular lipid droplet transfer promotes cadmium-induced mice nonalcoholic fatty liver disease. *J Haz Mater* 465:133151

Sun J, H Qu, W Ali, Y Chen, T Wang, Y Ma, Y Yuan, J Gu, J Bian, Z Liu (2023a). Co-exposure to cadmium and microplastics promotes liver fibrosis through the hemichannels-ATP-P2X7 pathway. *Chemosphere* 344:140372

Sun J, Y Chen, T Wang, W Ali, Y Ma, Y Yuan, J Gu, J Bian, Z Liu, H Zou (2023b). Cadmium promotes nonalcoholic fatty liver disease by inhibiting intercellular mitochondrial transfer. *Cell Mol Biol Lett* 28:87

Taganov KD, MP Boldin, K Chang, D Baltimore (2006). NF-κB-dependent induction of microRNA miR-146, an inhibitor targeted to signaling proteins of innate immune responses. *Proc Natl Acad Sci* 103:12481–12486

Togo S, UM Polanska, Y Horimoto, A Orimo (2013). Carcinoma-associated fibroblasts are a promising therapeutic target. *Cancers* 5:149–169

Triner D, YM Shah (2016). Hypoxia-inducible factors: A central link between inflammation and cancer. *J Clin Invest* 126:3689–3698

Tsujimoto S, M Kishina, M Koda, Y Yamamoto, K Tanaka, Y Harada, A Yoshida, I Hisatome (2016). Nimesulide, a cyclooxygenase-2 selective inhibitor, suppresses obesity-related non-alcoholic fatty liver disease and hepatic insulin resistance through the regulation of peroxisome proliferator-activated receptor. *Intl J Mol Med* 38:721–728

Tu C, Y Hu, P Zhou, X Guo, C Gu, Y Zhang, A Li, S Liu (2021). Lactate and TGF-*β* antagonistically regulate inflammasome activation in the tumor microenvironment. *J Cell Physiol* 236:4528–4537

Tunio S, FA Ujjan, M Memon, SA Fazlani, FA Kiani (2024). Research progress of cadmium toxicity on male reproduction health. *J Biomed Sci Biotechnol Res* 2:1–6

Ujjan IAI, JK Zaman, NH Kalhoro, AH Mirani, AL Bhutto, AN Khosa, B Sahito, C Wajid, A Babar, Z Abddin (2021). Screening of methicillin resistant *Staphylococcus aureus* from dogs and cats in Hyderabad Pakistan. *Pure Appl Biol* 10:969–977

Vadovics M, J Ho, N Igaz, R Alföldi, D Rakk, É Veres, B Szücs, M Horváth, R Tóth, A Szücs, A Csibi, P Horváth, L Tiszlavicz, C Vágvölgyi, JD Nosanchuk, A Szekeres, M Kiricsi, R Henley-Smith, DL Moyes, S Thavaraj, R Brown, LG Puskás, JR Naglik, A Gácserl (2022). *Candida albicans* enhances the progression of oral squamous cell carcinoma *in vitro* and *in vivo*. *MBio* 13:e0314421

Vanni C, M Ognibene, F Finetti, P Mancini, S Cabodi, D Segalerba, MR Torrisi, S Donnini, MC Bosco, L Varesio (2015). Dbl oncogene expression in MCF-10 A epithelial cells disrupts mammary acinar architecture, induces EMT and angiogenic factor secretion. *Cell Cycle* 14:1426–1437

Vidal AC, LE Howard, DM Moreira, R Castro-Santamaria, GL Andriole, SJ Freedland (2015). Aspirin, NSAIDs, and risk of prostate cancer: Results from the REDUCE study. *Clin Cancer Res* 21:756–762

Vistro WA, Y Zhang, M Azhar, R Wu, S Yang, C Chen, B Ding, W Qu, X Bai, Y Huang (2020). Hematological and plasma biochemical parameters of chinese soft-shelled turtle during hibernation and non-hibernation. *Intl J Agric Biol* 23:529–533

Vistro WA, Y Huang, X Bai, P Yang, Al Haseeb, H Chen, Y Liu, Z Yue, I Tarique, Q Chen (2019). *In vivo* multivesicular body and exosome secretion in the intestinal epithelial cells of turtles during hibernation. *Microsc Microanal* 25:1341–1351

Vistro WA, Y Zhang, X Bai, P Yang, Y Huang, W Qu, AS Baloch, R Wu, I Tarique, Q Chen (2019). *In vivo* autophagy up-regulation of small intestine enterocytes in chinese soft-shelled turtles during hibernation. *Biomolecules* 9:682

Wajid C, AH Baloch, AN Khosa, HA Kaleri, N Bangulzai, SA Fazlani, H Sadia, S Kalsoom, MB Arain, WA Vistro (2022). Prop-1 gene a selective marker of wool production in sheep breeds of Balochistan Pakistan. *J Anim Health Prod* 10:238–44

Waldhauer I, A Steinle (2008). NK cells and cancer immunosurveillance. *Oncogene* 27:5932–5943

Waldman AD, JM Fritz, MJ Lenardo (2020). A guide to cancer immunotherapy: From T cell basic science to clinical practice. *Nat Rev Immunol* 20:651–668

Wang S, L Yu, G Sun, Y Liu, W Hu, Y Liu, T Peng, X Wang, J Cheng, A Sr, B Qin. H Lu (2020). Danhong injection protects hemorrhagic brain by increasing peroxiredoxin 1 in aged rats. *Front Pharmacol* 11:346

Wang X, K Zhang, W Ali, J Li, Q Huang, D Liu, G Liu, D Ran, Z Liu (2024). Luteolin alleviates cadmium-induced metabolism disorder through antioxidant and anti-inflammatory mechanisms in chicken kidney. *Poult Sci* 103:103817

Wang Z, B Yang, M Zhang, W Guo, Z Wu, Y Wang, L Jia, S Li, SJ Caesar-Johnson, JA Demchok (2018). lncRNA epigenetic landscape analysis identifies EPIC1 as an oncogenic lncRNA that interacts with MYC and promotes cell-cycle progression in cancer. *Cancer Cell* 33:706–720

Würtz ET, J Hansen, OD Røe, Ø Omland (2020). Asbestos exposure and haematological malignancies: A Danish cohort study. *Eur J Epidemiol* 35:949–960

Xiao L, M Mochizuki, T Nakahara, N Miwa (2021). Hydrogen-generating silica material prevents UVA-ray-induced cellular oxidative stress, cell death, collagen loss and melanogenesis in human cells and 3D skin equivalents. *Antioxidants* 10:76

Xu W, J Tao, W Zhu, W Liu, A Anwaier, X Tian, J Su, G Shi, H Huang, G Wei, C Li, Y Qu, H Zhang, D Ye (2021). Comprehensive multi-omics identification of interferon-γ response characteristics reveals that RBCK1 regulates the immunosuppressive microenvironment of renal cell carcinoma. *Front Immunol* 12:734646

Yi H, Y Zhang, X Yang, N Wang, Y Zhang, Y Song, Chen, J Lian (2020). Hepatitis B core antigen impairs the polarization while promoting the production of inflammatory cytokines of M2 macrophages *via* the TLR2 pathway. *Front Immunol* 11:535

Yu M, X Zhang, H Li, P Zhang, W Dong (2017). MicroRNA-588 is downregulated and may have prognostic and functional roles in human breast cancer. *Med Sci Monit: Intl Med J Exp Clin Res* 23:5690-5696

Yu SY, SW Wang, TL Hwang, BL Wei, CJ Su, FR Chang, YB Cheng (2018). Components from the leaves and twigs of mangrove *Lumnitzera racemosa* with anti-angiogenic and anti-inflammatory effects. *Marine Drugs* 16:404

Yuan Z, Y Li, S Zhang, X Wang, H Dou, X Yu, Z Zhang, S Yang, M Xiao (2023). Extracellular matrix remodeling in tumor progression and immune escape: from mechanisms to treatments. *Mol Cancer* 22:48-67

Zhang K, J Li, W Dong, Q Huang, X Wang, K Deng, W Ali, R Song, H Zou, D Ran (2024). Luteolin alleviates cadmium-induced kidney injury by inhibiting oxidative DNA damage and repairing autophagic flux blockade in chickens. *Antioxidants* 13:525

Zhang K, J Li, W Dong, Q Huang, X Wang, K Deng, W Ali, R Song, H Zou, D Ran, G Liu, Z Liu (2020). The long non-coding RNA DANCR regulates the inflammatory phenotype of breast cancer cells and promotes breast cancer progression *via* EZH2-dependent suppression of SOCS3 transcription. *Mol Oncol* 14:309–328

Zou H, W Ali, K Deng, Y Chen, J Sun, T Wang, Y Ma, Z Liu (2024). The protective effect of luteolin on cadmium induced liver intestinal toxicity in chicken by Gut-liver axis regulation. *Poult Sci* 103:104242

Zhou H, F Wang, H Chen, Q Tan, S Qiu, S Chen, W Jing, M Yu, C Liang, S Ye (2016). Increased expression of long-noncoding RNA ZFAS1 is associated with epithelial-mesenchymal transition of gastric cancer. *Aging* 8:2023

Zhu J, Y Ma, J Wang, Y Wang, W Ali, H Zou, H Zhao, X Tong, R Song, Z Liu (2023). The mechanism of osteoprotegerin-induced osteoclast pyroptosis *in vitro*. *Intl J Mol Sci* 24:1518

Zou G, X Zhang, L Wang, X Li, T Xie, J Zhao, J Yan, L Wang, H Ye, S Jiao (2020). Herb-sourced emodin inhibits angiogenesis of breast cancer by targeting VEGFA transcription. *Theranostics* 10:6839-6853