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Immunological Processes in Cancer: A Link Between Inflammation and Immunity

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Abstract: Cancer is a worldwide issue and one of the most relevant death causes in child and adults. There are several causes that can lead to cancer development. It is well known that inflammation is one known hallmark of cancer and it favors tumor cells growth. Several alterations in immunological and inflammatory processes are caused in response to tumor presence and both innate and adaptive immunity have effective mechanism to destroy tumor cells. Nevertheless, distinct tumor types developed mechanisms to evade anti-tumor immunological responses. Here, we revise researches regarding inflammation and immune response during cancer development, as well as cancer signaling pathways and immunotherapy that have been performed in Brazil. The better understanding of the mechanisms regarding cancer and immunological processes is of huge importance and it may support the development of new cancer targets.

Keywords: Cancer, Inflammation, Immune Response, Cancer Signaling, Immunotherapy

Introduction

Cancer is considered a worldwide health issue. According to World Health Organization (WHO, 2014), deaths by malignant neoplasms reached a population of 7, 583, 252 and its incidence increased 20% in all world. Developing countries are the most affected ones by the disease and Brazil is among them. Brazil has a total population of 199,000,000 and WHO estimates a death rate by malignant neoplasm of 125 per 100,000 for men and 101 per 100,000 for women.

The Instituto Nacional do Câncer (INCA, 2014) estimates a rate of 576,000 new cases of cancer in Brazil for 2014, available for 2015. Among them, for male population, prostate cancer is the main neoplasm (70.42 new cases per 100,000 men), followed by lung cancer (16.79 new cases per 100,000 men) and colon cancer (15.44 new cases per 100,000 men). For female population, breast cancer is the most frequent malignancy (56.09 new cases per 100,000 women), followed by colon cancer (17.24 new cases per 100,000 women) and cervical cancer (15.33 new cases per 100,000 women).

Despite the large significance of health issues, the Brazilian general government expenditure on health as a percentage of total expenditure on health is of 45.7, while the general government expenditure on health as a percentage of total government expenditure is of 8.7 for the year 2011 (WHO, 2014).

Inflamation and Cancer

Inflammation is a well-known hallmark of cancer. About 20% of cancer deaths can be related to inflammation and infection (Osório-Costa *et al.*, 2009). The seven hallmarks of cancer includes cancer-related inflammation, enable the replicative immortal, resist to cell death, sustain a proliferative signaling, evade growth suppressors, induction of angiogenesis and activate invasion and metastasis. As well, it is known that chronic inflammation is associated with increased risk of cancer development and an inflammatory microenvironment favors proliferation of mutated cells during initiation. The tumor microenvironment is surrounded by innate immune cells, adaptive immune cells, cancer cells and stroma. It is also stated that there is a strong association between immune system and tumor during every step of its development (Fan *et al.*, 2013).

Therefore, the nexus among inflammation, immune system and cancer is well strait. Thus, this article aims to review new insights related to inflammation and cancer, as well as the importance of immune system response and cellular signaling during tumor development and

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immune therapies focusing in research of Brazilian laboratories, a developing country.

The Role of Inflammation in Cancer Development

Rudolf Virchow, a German doctor, who is considered the father of modern pathology, first proposed a relationship between inflammation and cancer. Virchow showed that leukocytes were present in malignant tissue, stating that tumors arise from chronic inflammatory sites. As suggested by Balkwill and Mantovani (2001), the inflammatory cells and cytokines found in tumors may contribute more to tumor development than to host antitumor response.

Distinct tumor types display distinct inflammation grades. Viana *et al.* (2013) inoculated melanoma, colon and mammary cancer cells in the flank of syngeneic mice. The assessed tumors displayed different grades of inflammation and angiogenesis. Among them, mammary tumors exhibited the higher inflammatory content and melanoma was the most angiogenic.

Panis *et al.* (2012a) reported that in early (TNM-tumor, node, metastasis- I and II) and advanced (TNM III and IV) stages of human breast cancer there is an increase in C reactive protein levels, indicative of increased inflammatory activity as compared to matched healthy individuals. They also showed increased of the pro-inflammatory cytokines TNF-α (tumor necrosis factor alpha) and IL-1β (interleukin 1β) in the advanced stages of the disease. Concerning data indicate us that in breast cancer are observed an enhancement of pro-inflammatory markers during tumor development. Nevertheless, Panis *et al.* (2012b) showed that the enhancement of the pro-inflammatory cytokines TNF-α and IL-1β in human breast cancer is inhibited after chemotherapy treatment with doxorubicin. Herrera *et al.* (2012) also characterized the inflammatory status of distinct molecular subtypes of breast cancer patients and found a correlation between clinical data and inflammatory findings. Likewise, the inflammatory status differs among the distinct molecular subtypes of breast cancer, which is of great significance for future treatments.

The anti-inflammatory status in cancer has also been reported. Jorge *et al.* (2013) showed increased expression of anti-inflammatory protein annexin I and also galectin 1, in human gastric cancer. Yoshimoto *et al.* (2012) demonstrated that the Hh (Hedgehog) pathway activation, which is involved in processes like cell survival and proliferation, has anti-inflammatory and anti-apoptotic effects on colon cancer cells and it is a key controller of the cells function.

Regarding data from Brazilians laboratories, it is clear that inflammatory response may depends on its kind of tumor and the response favors tumor development. The results show that tumors displays distinct grades of inflammatory profile and even tumor grade or subtype are responsible for a diverse response.

The Influence of Obesity in Cancer Development

It is well known that obesity increases sex and metabolic hormones and inflammation. Therefore, obesity may be related to the increased risk rate of several types of cancer and disease outcome (Osório-Costa *et al.*, 2009). Adipose tissue regulates the body energy homeostasis secreting cytokines, hormones and inflammatory markers, together called adipokines. The inflammatory process in obesity comprises activation of JNK (c-Jun N-terminal kinase) and NF-κB (factor nuclear kappa B). The expansion of adipose tissue is combined to infiltration of several types of innate and adaptive immune cells, both secreting pro-inflammatory markers that may favor tumor development. Angiogenesis may be also regulated by adipocytes through production of leptin, TNF-α, IL-6, IL-8, VEGF (vascular endothelial growth factor) and TGF-β (transforming growth factor beta) (Catalán *et al.*, 2013).

Flores *et al.* (2012) showed that obesity increased the size and incidence of colorectal cancer. In their research model, an inflammatory state was observed in the colon of obese mice. Moreover, increased TNF-α derived from adipocytes and macrophages of adipose tissue accompanied by increased IKK-β (inhibitor of nuclear factor kappa-B kinase subunit beta) phosphorylation, decreased IκBα (inhibitor of kappa B) expression, increased JNK and c-jun phosphorylation in colonic tissues were observed. Also, genetic obesity promoted colon carcinogenicity associated with inflammation.

Bozza and Viola (2010) revised the role of lipid droplets in inflammation and cancer. Lipid droplets are endoplasmic reticulum-derived organelles expressed in fat-storing cells. Several studies emerged showing increased number of cytoplasmic lipid droplets in inflammatory and neoplastic process and that they can be regulated in cell activation and metabolism. Also, lipid droplets are sites for eicosanoids formation, which has key role in inflammation and cancer. This organelle has a role in cell metabolism and proliferation as mediating signaling of PI3K (phosphoinositide 3-kinase), ERK1 (extracellular signal regulated kinase), ERK2, p38 and Protein Kinase C (PKC). Employing animal model of obesity, Ribeiro *et al.* (2012) found increased epithelium and stroma cell proliferation and PI3K in prostate of obese rat as compared to non-obese.

Adiponectin has been employed as important media-tor also in non-overweight women bearing breast cancer. Panis *et al.* (2014) showed a decrease in adiponectin levels in non-obese breast cancer patients compared to non-obese healthy women. Also, after 2 cycles of chemotherapy treatment, adiponectin levels increases significantly demonstrating a great chemotherapy response. Moreover, adiponectin levels were altered during disease outcome.

The several results regarding inflammation and obesity report its relation with cancer. The emerging data show us the great importance of the inflammatory status observed in obese individuals as a potent site for arising tumors.

The Immune System

The process of tumor elimination encompasses both innate and acquired immunity, leading to an integrated host defense against tumors in which various cells and molecules mutually work. Innate immunity is the first line of host defense against pathogens and tumor cells. The major cell types involved in innate immune response includes Natural Killer (NK) cells and macrophages. The adaptive immune response is involved in the elimination of invading microorganisms and host defense in later stages of tumor growth. The adaptive immune response includes T lymphocyte as specific cell type and against tumor antigens responsible for immune memory (Ramos *et al.*, 2013; Lehrnbecher *et al.*, 2008; Loose and Wiele, 2009). Tumors can evade the immune system by a variety of mechanisms. Their ability to interfere with immune cells is one of the main reasons for the host failure to control tumor suppression (Dunn *et al.*, 2004).

Innate Immune System and Cancer

Innate immunity is associated with the early stages of the immune response and acts against the pathogenic agent in a non-specific way, suffering no alteration with repeated exposure to this agent (Janeway and Medzhitov, 2002). Innate immune response is sustained by cells such as neutrophils, eosinophils and mast cells, constituting the first line of defensive response (Davoine *et al.*, 2013). The tumor development is controlled mainly by cytokines (interferon-IFN, IL and TNF), macrophage and NK cells. As the immune system is stimulated first, there is activation and recruitment of inflammatory cells and lymphocytes through the release of cytokines and specific chemokine (Shi *et al.*, 2003).

The recognition and lyses of tumor cells by NK cells are extremely important in innate immunity against tumors. Since their discovery, a large number of studies have demonstrated that NK cell-mediated lyses of different types of tumor cells in vitro, as well as NK cell-dependent elimination of many tumors in vivo (Ljunggren, 2008). NK cells are capable of inducing lyses of cells showing decreased expression of MHC (major histocompatibility complex) class I on their surface (e.g., tumor cells). The decrease of MHC I molecules on the cell surface prevents it to be recognized and lysed by specific CD8+ (cluster of differentiation) T lymphocytes. In this context, the function of NK cells becomes necessary in combating carcinogenesis

(Garay *et al.*, 2007; Maccalli *et al.*, 2009). Once activated, NK cells release several cytokines, especially IFN-γ. Moreover, NK cells release perforin inducing pores formation in tumor cells during the process of cytotoxicity, similarly to that played by CD8+ T lymphocytes (Abbas *et al.*, 2011; Maccalli *et al.*, 2009). NK cells also produce TNF-α, TNF-β and GM-CSF (granulocyte macrophage-colony factor) stimulant (Vivier *et al.*, 2011). NK cells express CD56 and CD16. Dalmazzo *et al.* (2009) associated the expression of CD56/CD16 with worse prognosis for T-cell acute lymphoblastic leukaemia.

Regarding innate immune system, macrophages also play a central role in fighting neoplastic cells. Macro-phages activation occurs through the recognition of anti-gens on the tumor surface or, indirectly, by the production of IFN-γ by specific-T lymphocytes. After maturation and expression of co-stimulatory molecules on the surface, these cells produce several cytokines, release lysosomal enzymes and Reactive Oxygen Species (ROS) to destroy tumor cells. These cells also produce large amounts of TNF-α, which induces apoptosis of tumor cells through the activation of effector caspases coupled via TNF receptor (Dudley *et al.*, 2002; Sica *et al.*, 2008, Maccalli *et al.*, 2009).

Inflammation status present in the tumor microenvironment is characterized by leukocyte infiltration, which varies in subset composition and distribution (Liotti *et al.*, 2012). Cancer cell recruit monocytes from circulation. Herein, monocytes are induced to differentiate into macrophages by chemotactic factors (Vendramini-Costa and Carvalho, 2012). Phenotypically, macrophage can be recognized by the expression of CD68. Functionally, there are two different subsets of macrophages population: M1 and M2. M1 main function is phagocytes is in response to bacterial stimuli and/or Th1 (T helper) cytokines and it is highly pro-inflammatory, while the main function of M2 is immune suppression and trophic activity in response to Th2 cytokines and it presents an anti-inflammatory profile (Mantovani *et al.*, 2002; Caillou *et al.*, 2011). Therefore, the tumor associated macrophages may acts in host defense or in tumor defense according to its phenotype (Becker *et al.*, 2013).

Researches aiming to characterize M1 and M2 population in tumors have been recently developed in Brazil. Costa *et al.* (2013) showed a predominance of M2 phenotype in the tumor microenvironment of oral cavity squamous cell carcinoma characterized by higher percentage of macrophages expressing IL-10 and TGF-β compared with healthy individuals. The predominance of M2 phenotype was related to local immunosuppression and reduced survival. Similarly, Lepique *et al.* (2009) also showed a predominance of M2-like macrophages in HPV (human papiloma virus) 16-associated tumors leading to a suppression of antitumor T-cell response, as

a higher level of IL-10 was produced. Thus, this phenotype favors tumor growth and should be considered for immunotherapy interventions.

Adaptative Immune and Cancer

After the induction of the first line of host defense, the interactions between mature Antigen-Presenting Cells (APCs) and cytokines lead to a more efficient and targeted immune response. The cells of acquired immune response, such as B lymphocytes, T lymphocytes and leukocytes are distinguished from innate immunity by expression of antigen receptor produced by genetic rearrangements (De Visser *et al.*, 2006). The interaction of tumor cells with the immune system plays a crucial role in the process of carcinogenesis (Dranoff, 2004).

The immune response against cancer cells has been shown to involve a tight balance of cytokines. Further-more, depending on the type and levels of secreted cytokines, lesion progression or regression may be improved. It is for a long known that the complex cytokine network that participates in the immune response is controlled by genetic programs (Mossmann *et al.*, 2005).

Cytokine production derives mainly helper cells (e.g., CD4+) that are central of a successful immune response. Naive CD4+ T cells differentiate into one, of at least four, functionally distinct forms: Th1, Th2, Th17 and Tregs (regulatory T cells). Th1 cells secrete cytokines involved in the activation of a cellular response, whereas Th2 cells promote mainly the development of a humoral immune response. In general, Treg are identified as FoxP3+ (forkhead box P3) lymphocytes and is thought to contribute to tolerance of tumor specific T cells (Zhou and Levitsky, 2007; Josefowicz and Rudensky, 2009). The cytokines produced by the Treg profile has been described as potent inhibitors of antitumor immune re-sponse and are associated with poor prognosis for many types of cancer (Hiraoka *et al.*, 2006; Downey *et al.*, 2007; Fecci *et al.*, 2007; Fu *et al.*, 2007). The discovery of Th17 cells and their role in protecting the host against infectious agents and pathogenesis of several inflammatory and autoimmune diseases resulted in the raise of immunological research and its role in human cancer is still under investigation (Park *et al.*, 2005; Yang and Ansell, 2009; Su *et al.*, 2010).

In the past few years, a great number of researches have been published in Brazil regarding immune response and cancer.

The review conducted by Watanabe *et al.* (2010) shows that although T cells present the most important immunological response in tumor growth in the early stages of cancer, they become CD4+ and CD8+ suppressive Tregs after chronic stimulation and interactions with tumor cells, thus promoting cancer development and progression. Ramos *et al.* (2013) revised the role of Tregs during cancer development.

The Treg-mediate suppressive activity may contribute to the immune evasion of tumors. During tumor development, the systemic tolerogenic status of DCs (dendritic cells) is favored in-creasing the recruitment of Tregs. The mechanisms which DCs recruit Tregs remains to be elucidated.

Peghini *et al.* (2012) reported that in cervical intraepithelial cancer bearing women, with no co-infection, the tumor progression was dependent on suppression of cellular immunity, as characterized by a Th1 cytokine response and development of an immunosuppressive Treg profile for neoplastic progression. Thus, an imbalance in cytokine appears to be the major mechanism by which tumor cells could escape of the immune surveillance system to facilitate the tumor progression.

The investigation about the inflammatory infiltrate and characterized the Tregs and Th17 cells in patients with invasive ductal carcinoma of the breast was per-formed by Benevides *et al.* (2013). The authors found a decrease in T-cell proliferative response in breast cancer patients that could be related to the increased frequency of Tregs found in the circulation. The increased frequency of Tregs cells found in the tumor microenvironment was associated with the tumor aggressiveness and its increased presence may occur in response to the C-C motif Ligand 22 (CCL22) chemokine. Moreover, higher messenger RNA (mRNA) expression of IL-10 and TGF-β was found in the breast tumor that could contribute to differentiation and functionality of Tregs. Regarding Th17 cells, authors reported also an increased mRNA expression of IL-17A and accumulation of Th17 cells within the tumor that may contribute to cancer development.

Cunha *et al.* (2012) found increased immune cells in-filtrating in the malignant tissue of patients with differentiated thyroid carcinoma than in benign lesion. They observed increased Th17 and Tregs cells in the malignant tissue associating with favorable prognostic features.

The role for Tregs in oral squamous cell carcinoma was reported by Gasparoto *et al.* (2010). The authors showed the presence of Tregs in oral squamous cell car-cinoma lesions and in the peripheral blood mononuclear cell from patients, where Tregs seem to act as suppressor of immune system response. Also, Carneiro *et al.* (2013) showed that increased TGF-β secretion in oral squamous cell carcinoma may be due to a C allele, suppressing antitumor immune response and affecting the risk rate of this carcinoma. Ramos *et al.* (2012a) showed the importance of Tregs in murine squamous cell carcinoma. The authors suggest that Tregs blockage impairs the tu-mor progression by modulating the immune response in tumor microenvironment. Thereby, it is evident that the established Th17 and Tregs profile acts in tumor favor, leading to tumor progression and growth.

The main players of innate and adaptive immunity are DCs (Banchereau *et al.*, 2000). DCs are highly potent APCs and they are able to migrate into the lymph nodes and present antigens to naive T lymphocytes and thus induce a cellular immune response involving CD4+ Th1 cells, cytotoxic CD8+ T cells and B cells (Schott, 2006). Since DCs can modulate the whole immune repertoire, these cells are essential in the understanding of inflammatory tumor microenvironment. The production of immunosuppressive cytokines as IL-10 and VEGF in the tumor microenvironment can inhibit the DC function by inhibiting effector T cell response and increasing regulatory T cells function (Gabrilovich, 2004). Immature DCs recognizes PAMPs and DAMPs (pathogens or danger-associated molecular patterns, respectively) and migrates to lymphoid organs and activates T lymphocytes. They induce T cell tolerance to antigens acquired in healthy tissue and has key role in the prevention of autoimmunity (Ramos *et al.*, 2013).

There are many research embracing DCs and cancer being developed in Brazil. Matias *et al.* (2013) showed that the autologous DC vaccine stimulated the immune cells from the peripheral blood of patients with cancer and generally increased the production of Th1 cytokines, which are related to immune-modulatory responses against cancer. Baleeiro *et al.* (2008) analyzed the microenvironment of primary lung cancer and found that in the tumor-affected lung there was a higher incidence of immature DCs and TNF-α positive cells, thus influencing an effective immune response against tumor. CD83 is a marker of DC maturation. Borges *et al.* (2011) evaluated the expression of CD83 in breast cancer tissue. CD83 expression was analyzed in histopathological samples of the breast by immunohistochemistry and its expression was greater in fibroadenoma than in adjacent breast tissue. Also, Ramos *et al.* (2012b) showed that breast cancer patients displayed altered phenotype of monocyte-derived DCs, which induces preferentially Tregs.

Data from diverse research laboratories converge to the knowledgement that the tumor presence induces several stimuli to inflammatory and immunological changes to favor its growth and development. Also, there is increased incidence of cancer among patients who developed immunodeficiencies (Block and Markovic, 2009). The understanding of the mechanism by it occurs involves several stimuli and a complex cellular signaling. In the next topic, main cellular signaling involved in tumor development will be performed.

Cancer Signaling Pathways

The understanding of cellular signaling pathways and cellular interactions of cancer development is of extremely importance. For this purpose, Acencio *et al.* (2013) developed a new computational approach for investigation in cancer research for detecting signaling networks.

The NF-κB and Signal Transducer and Activator of Transcription 3 (STAT3) play key role linking inflammation to cancer (Fan *et al.*, 2013). As revised by Osório-Costa *et al.* (2009), the NF-κB signaling pathways have important role in immunity and inflammation. Several stimuli can induce NF-κB transcription factors activation, mediating immune and inflammatory responses, developmental processes, cellular growth and survival. NF-κB may promote cell proliferation, suppresses cell death, can control cell cycle regulatory genes and interacts with PI3K-AKT-mTOR (mammalian target of rampamycin) signaling pathway (Fan *et al.*, 2013). Silva *et al.* (2013) revised important signaling pathways described for prostate cancer, the most frequent malignancy found in men. Among them, activation of NF-κB by canonical pathway plays important role in prostate cancer, as it is often constitutively activated due to increased levels of specific receptors like TNF receptors, leading to activation of genes involved in the development and progression of the tumor.

The STAT signaling transduction pathways is involved in the regulation of cellular growth, survival and differentiation. There are seven known mammalian STAT family members and STAT3 seems to have a particular role in inducing oncogenesis and maintaining a pro-carcinogenic inflammatory environment. Besides, STAT3 can suppress anti-tumor immunity by antagonizing the expression of anti-tumor Th1 cytokines and promoting tumor growth through Tregs expansion in tumor and the development of Th17 T cells (Fan *et al.*, 2013). In prostate cancer it is found to be constitutively activated inducing cell proliferation and apoptosis inhibition mediated by STAT3 activation (Silva *et al.*, 2013).

The PI3K/AKT (protein kinase B) pathway mediates cellular functions as cell survival, proliferation and differentiation. PI3K/AKT influences the action of ERKs favoring androgen receptor-independent growth and it can enhance the presence of stable metalloproteinase receptor favoring invasiveness and metastatic phenotypes of prostate cancer cells and in later stages of prostate cancer, Mitogen-Activated Protein Kinases (MAPK)/ERK signaling pathway seems to be also activated (Silva *et al.*, 2013).

Sgnaolin *et al.* (2013) described a function for B1 and B2 receptors in bladder cancer. B1 and B2 receptors are stimulated during inflammatory stimuli. Authors showed that B1 and B2 receptors stimulation induces cancer cell proliferation in vitro. The expression of B1 receptor in bladder cancer human biopsies and under conditions of chronic inflammation was also increased and it may represent a marker of tumor progression. Moreover, in this model, PI3K/AKT and ERK1/2 signaling pathways seem to be involved in the cell proliferation.

Toricelli *et al.* (2013) reported a Tissue Inhibitor of Metalloproteinase-1 (TIMP1) -CD63-β1 integrins containing-supramolecular complex in cell surface of melanoma cells. The over-expression of TIMP1 was shown

to be involved in the acquisition of anoikis-resistant phenotype in melanoma cells through PI3K signaling pathway independently of AKT activation.

A quinone induced- biochemical and morphological alterations of apoptosis in melanoma cells mediated by ROS was shown by Massaoka *et al.* (2012). They demonstrated that the antiproliferative and proapoptotic response observed with this quinone treatment were mediated by up-regulation of proapoptotic Bax, down-regulation of AKT and activation of p38 MAPK signal-ng pathways through ROS generation and it also induced mitochondrial depolarization.

Vidal *et al.* (2013) analyzed human papillary thyroid cancer specimens. They demonstrated that in the cancer tissue there was an increased expression and phosphory-lation of Adenosine Monophosphate Kinase (AMPK) signal.

Rossa *et al.* (2012) reported a role for Suppressor Of Cytokine Signaling 3 (SOCS3). Authors found a nuclear localization for SOCS3 in head and neck squamous cell carcinoma cell lines, where in non-cancerous cells it was located in cytoplasm. The induced-over-expression of SOCS3 in cancerous cells reduced proliferation, migration and invasion and, also, the decreased SOCS3 levels observed in cancerous cells is an early event suggesting that its loss may regulate the signaling involved in carcinogenesis.

In Brazil, a higher incidence of childhood adrenocor-tical tumors compared to others countries is found due to a higher frequency of R337H TP53 mutation. Letouzé *et al.* (2012) identified different patterns of oncogenic routes between southern Brazilian children and non-Brazilian children related to inheritance of the R337H TP53 mutation, loss of wild-type TP53 allele in the tumor and defective function of TP53 and genomic aberrations.

There are several signaling pathways altered in cancer signaling and many pathways involved during tumor development. Here, we revised the major pathways and the news researches developed in Brazil and found their particularly specificity for each tumor type. Again, it is observed that specific signaling pathway may be super-activated or inhibited by tumor signaling in order to favor tumors growth and development.

Immunotherapy in Cancer

The pillars of human cancer therapy have historically been surgery, radiotherapy and chemotherapy, but a fourth modality, immunotherapy (Kirkwood *et al.*, 2012), has been well documented since 1890 s by Coley, who treated sarcoma patients with bacterial preparations, commonly referred to as "Coley's toxin" (Coley, 1991). In the last decades a range of cancer therapies that exploit the complex interactions between tumors and immune cells has been studied by several research groups. Others studies have made significant progress in our knowledge of the immune system. Thus using all this information, scientists could create synthetic molecules to attack the tumor, or may help the immune system to do its job more effectively. Also, important, this improved the understanding of immunotherapy and about the mechanisms underlying immunity in cancer has fueled an expanding array of new therapeutic agents for a variety of cancers (Kirkwood *et al.*, 2012). Besides, it has also been suggested studies to evaluated the combination of immunotherapy to traditionals chemotherapies (Barrett and Blanc, 2009).

Table 1 summarizes several immunotherapies in clinical trials and in current use. Here, we focuses on active therapies and passive therapies using monoclonal antibodies.

Active Therapies

First, researches attempted to developed new thera-pies to increase immunity against tumors were based on non-specific stimulation.

One of the most effective therapies for cancer is the bladder intravesical Bacilo Camette Guérin (BCG) (Shah *et al.*, 2006). BCG for cancer immunotherapy activity may have its function enhanced by addition of IL10 blocking monoclonal antibody (Luo *et al.*, 2012). Favaro *et al.* (2012) published an interesting article where they compared and characterized the effects of intravesical BCG and/or staphylococcal enterotoxin B for non-muscle invasive bladder cancer. The results showed that both therapies presented similar anti-angiogenic effect and they observed additional activity compared to monotherapy. Also, it was more effective in restoring apoptosis and balancing cellular proliferation and it correlated with increased endostatin and decreased VEGF, matrix metalloproteinase-9, Ki-67 and insulin-like growth factor receptor-1 reactivity.

Macedo *et al.* (2009) described a case report about topical immunotherapy for the treatment of periocular basal cell carcinoma and showed that one year after treatment the patient showed no signs of disease recurrence. The Brazilian Journal of Oncology encloses two review articles about several reported tumor markers (Almeida *et al.*, 2007) and tumor markers in breast cancer (Eisenberg and Koifman, 2001) attempting for the importance of clinical diagnostics. Pacheco *et al.* (2002) reviewed the role of some traditionally known tumor markers (CEA, p53, NSE, K-ras) for lung cancer. Also, an interplay between the tumor marker p53 and p21 was shown to have a key role in colorectal cancer (Abdulamir *et al.*, 2008).

Onuchic *et al.* (2012) used a model of human melanoma cell lines to investigate the role of Pla-Quette Aggregation Factor Receptor (PAFR) and evaluate the mechanisms of microenvironment response. They showed that the treatment with cisplatin lead to increased expression of PAFR. The accumulation and inhibition of PAFR-dependent signaling pathways by a PAFR antagonist (WEB2086) seemed to chemo-sensitize melanoma cells in vitro, therefore constituting a promising target for combination therapy for melanoma.

Table 1. Current use and clinical trials for cancer immunotherapy

Cancer immunotherapy					Clinical development	References
Active	Specific	Vacines	Sipuleucel-T	Prostate cancer	Current use	Saied et al., 2014
			Dendritic cells-melapuldencel-T	Melanoma	Clinical trial	Anguille et al., 2014
			Dendritic cells-sipuleucel-T	Prostate	Clinical trial	Anguille et al., 2014
			Dendritic cells-DC-VAX-L	Brain	Clinical trial	Anguille et al., 2014
			PROSTVAC-VF/PSA-TRICOM, JBT 1001	Prostate cancer	Clinical trial	Westdorp et al., 2014
			MAGE-A3	Melanoma	Clinical trial	Kono, 2014
	Non-specific	Immuneadjuvants	BCG	Bladder cancer	Current use	Shah et al., 2006; Favaro et al., 2012
		Cytokines	interleukin-2	Melanoma	Clinical trial	Barker and Postow, 2014
Passive	Monoclonal Antibodies	Checkpoint blocking antibodies	Anti-cytotoxic T-lymphocyte antigen 4 (anti-CTLA-4) (ipilimumab)	Melanoma	Current use	Kyi and Postow, 2014
			Anti-cytotoxic T-lymphocyte antigen 4 (anti-CTLA-4) (tremelimumab)	Multiple cancers	Clinical trials	Kyi and Postow, 2014
			Anti-programmed death 1 receptor (anti-PD-1) (nivolumab)	Melanoma renal cell carcinoma, lung cancer	Clinical trial	Kyi and Postow, 2014
			Anti-GD2	Multiple cancer	Clinical trial	Ahmed and Cheung, 2014
			Anti-HER2 (trastuzumab)	Breast cancer	Current use	Mohit et al., 2014
		Co-stimulatory	Anti-CD40 monoclonal antibody (mAb) CP-870,893	Advanced solid tumors	Clinical trials	Ruter et al., 2010
	Adoptive immunotherapy	Adoptive cell transfer	Tumor Infiltrating Lymphocyte (TIL) + IL-2+ lymphodepletion	Melanoma	Clinical trial	Saied et al., 2014
			Nonmyeloablative chemotherapy + infiltration lymphocytes + interleukin-2	Melanoma	Clinical trial	Barker and postow, 2014

The new vessel formation is closely linked to neo-proliferation of cells by the bone marrow and contributes to tumor development. Pereira et al. (2008) described the role of endothelial cells in hematologic malignancies and reported the anti-angiogenic drug therapy with VEGF as the possible targets. In this model, the directly blocking of VEGFR prevented the mobilization and recruitment of these cells to tumor neovascularization. Another route could be the capacity of Endothelial Progenitor Cells (EPCs) and pro-angiogenic hematopoietic cells to release toxins into the tumor after migration and vascular adhe-sion, causing local toxicity (Rafii et al., 2002).

Vulcani-Freitas et al. (2011) accomplished the profile of gene expression of Preferentially Expressed Antigen of Melanoma (PRAME). PRAME was present in several tumors including medulloblastoma and it has low expression in normal tissue of patient samples. The PRAME gene was overexpressed in 84% of samples, allowing it to be a strong candidate for immunotherapy.

Paiva et al. (2013) published an article about onco-lytic virotherapy showing its innovative and highly promising route for treating cancer. Authors proposed a multi-scale mathematical model to study how the immune response interferes with the viral oncolytic activity. They concluded that given the complexity of tumor-stroma-immune system interactions, a mathematical modeling could help researches to evaluate quantitatively these strategies or even the result of their combination.

Favaro et al. (2012) characterized the effects of P-MAPA (Protein Aggregate Magnesium-Ammonium Phospholinoleate-Palmitoleate Anhydride) on TLRs in vitro and in vivo, as well as to assess its potential as adjuvant therapy for infectious diseases and cancer. The results evidenced that P-MAPA acted as TLR ligand in vitro and improved the immunological status in model for bladder cancer, increasing TLR2 and TLR4 protein levels. The results may encourage the further investigation of P-MAPA as a potential candidate for the treatment of cancer and infectious diseases.

Coppin et al. (2005) compiled articles that evaluated immunotherapy for advanced renal cell carcinoma comparing administration of high-dose interleukin versus other options and IFN-α administration against other options. The authors concluded that IFN-α provided a modest survival benefit compared to other commonly used treatments. In patients with metastases at diagnosis with minimal symptoms, nephrectomy followed by IFN-α gave the best survival strategy and it is fully validated therapies.

Vaccines

Vaccines are developed from cancer cells, parts of cells or antigens (Elert, 2013) and it can be administrated with adjuvants in order to improve the response (Capitini et al., 2009). DCs are the most potent antigen presenting cells and it has been used as vector in the construction of vaccines (Palucka and Banchereau, 2013; Diniz and Ferreira, 2010). DCs not only induce protection against pathogens, but also increase immunity in various diseases, such as cancer (Melief, 2008). It is believed that the administration of different forms of antigens (DNA, RNA, proteins, peptides, viruses, cell lysates) as a vector together with DCs, increases the immunity from presentation to T lymphocytes (Pinho et al., 2013) and Tregs (Ramos et al., 2013).

Among the several cancer types testing DCs as vector vaccine, melanoma is the most studied (Ellebaek et al., 2012), followed by human breast

cancer, human leukae-mia and human glioblastoma (Romagnoli *et al.*, 2013). Antunes *et al.* (2006) reported a case of a 66 years old woman with renal cell carcinoma with sarcomatous differentiation. They reported that 3.5 years after radical nephrectomy and DC vaccination there was a retroperitoneal pure sarcomatous recurrence of the tumor.

Dall'Oglio *et al.* (2011) treated two male patients with metastatic renal cell carcinoma with DC vaccine immediately after surgery and standard treatment. After 9 and 10 months, the patients showed a stable disease. Thereby, DC treatment seems to be a potential vaccine in the cancer treatment.

Most of the experiments comprise the isolation of DCs *in vitro* and later loading with these with tumor antigens. However, several types of antigens have been tested. Among them, it can be mention the antigens de-rived from apoptotic or necrotic tumor cells, tumor cell lysates, synthetic peptides and MHC class I restricted DNA or RNA coding for tumor antigens (Banchereau *et al.*, 2001).

Immunological adjuvants that induce T cell-mediate immunity comprising the least side effects are needed for the development of human vaccines. Thus, Junqueira *et al.* (2012) used a melanoma mouse models to investigate the role of antigens derived of plasmatic membrane of the Trypanosoma cruzi as immunological adjuvants in an antitumor vaccine. Obtaining favorable results, the antigens of *Trypanosoma cruzi* were considered an efficient immunological adjuvant. Thus, parasite adjuvants should be further explored in the development of vaccine formulations, aiming to induce both humoral and cellular mediated immune responses.

Monoclonal Antibodies

During the last decade, the clinical use of monoclonal antibodies was effective and antibodies are now the frontline in the treatment of cancer. The antibodies have the unique ability to recognize surface antigens ex-pressed on tumor cells, target them and kill tumor cells while simultaneously activating the immune response to attack tumor cells through the complement cascade or Antibody-Dependent Cellular Cytotoxicity (ADCC) conferring specificity and minimizing adverse effects (Shuptrine *et al.*, 2012; Weiner *et al.*, 2012).

In Brazil, a review about the use of monoclonal antibodies for diagnosis and therapy of squamous cell carcinoma of the head and neck was first published Gripp *et al.* (1994). Emphasizing the clinical analysis about immunoglobulin IgY, the main antibody produced by hens (Gallus domesticus), Silva and Tambourgi (2010) presented an overview of the generation, structure and properties of IgY, as well as the advantages of chicken antibodies use over mammalian antibodies in immunodiagnostics and immunotherapy.

Conclusion

For a long time inflammatory processes have been recognized to contribute to cancer development. Since then, several research groups evolve in order to unveil the mechanisms by it occurs. It is also known that immunological processes have an important role in tumor destruction. Thus, this review shows several mechanisms studied in Brazil by which tumor acts in its own favor. Some of them acts increasing a Th2 profile and inducing Tregs cells in tumor microenvironment. Also, several signaling pathways related to tumor growth, development, resistance, differentiation, survival and proliferation are strongly activated. Thereby, many researches are focusing in new approaches for cancer immunotherapy, which aims to amplify the host immunological response against tumors. As stated, non-specific therapies, monoclonal antibodies and vaccines constitute the main kinds of immunotherapy. The analyzed articles here cited may help to better understand the state of the art regarding cancer, inflammation and immunity. Despite we are far from the completely understand of the mechanisms by which tumor cells influence the complex host response, we hope to highlight the insights to new researches in the field with consequent improvement of target cancer immunotherapies.

Author's Contributions

All authors equally contributed in this work.

Ethics

This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and no ethical issues involved.

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