Chapter 12
Modulation of Tumor Immunity by Medicinal Plant or Functional Food-Derived Compounds

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12.1 Introduction

Most conventional cancer treatments rely heavily on compounds that directly target cancerous cells. However, noncancerous stromal components, most of which are immune cells, constitute as much as 50% of the cancer "tissue" and play a critical role in cancer progression. This leaves an open window for possible atypical adjuvant therapy in the form of naturally derived compounds that target the mechanism for cancer/stromal (immune) interaction. Research into natural compounds may illuminate hidden potentials and offer possible breakthroughs in more effective cancer treatment.

By administering compounds which modulate a proper immune response, we also provide the powerful tool of an additional and alternate avenue to target cancer. Unilateral treatment, targeting only the proliferating cancer cells, has shown to result in chemoresistant forms of cancer (Chang 2011). Thus, by discovering and utilizing secondary or tertiary adjuvant treatments, successful elimination of cancer could be achieved without causing unnecessary harm to patients, could be achieved. Naturally derived compounds have one characteristic that should be emphasized, and that is the lack of injurious side effects when taken in therapeutic doses (Storka et al. 2015).

The importance of the immune system and the central role it plays in eradicating newly forming cancer from the body should be greatly emphasized. As most cancer therapeutics target the rapidly dividing property of cancer cells, they will also destroy rapidly dividing normal cells, such as the bone marrow cells and hair

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follicles. A proper antitumor immune response is capable of specifically recognizing and eliminating cancer cells, including ones that have infiltrated into normal tissue or metastasized into distant organs—tumor cells that are often missed by conventional therapeutics. However, continual expression of particular immune responses, i.e., inflammation, can actually aid in the progression of cancer via various mechanisms (Grivennikov et al. 2010).

Inflammation is a normal response to different forms of tissue assault or injury. It is necessary in certain pathological states to allow the body to mount defense and eventual repair, e.g., combatting extracellular pathogens (Singer and Clark 1999). The activation of the innate immune system and subsequent Th2 response aid in production of inflammatory molecules and eradication of the pathogen (Damsker et al. 2010; Kaiko et al. 2008). In case of cancer, neoplastic cells send out danger signals in the form of hypoxia-inducible factor (HIF), heat-shock proteins (HSPs), or high mobility group box 1 (HMGB1) protein, which may lead to a cytotoxic, antitumor immune response or a prolonged/chronic inflammation resulting in an advantageous environment for tumor progression (Tsan 2006). Studies have concluded that interfering with chronic inflammation and eliciting a cytotoxic response can reverse the pro-tumorigenic environment, and therefore provides an ideal target for adjuvant therapy. Research has shown that many food- and plant-derived molecules can greatly benefit cancer patients by directly inhibiting inflammation (Zubair et al. 2017). These compounds potentially work by altering the expression of certain signal transduction pathways within immune system, which would help prevent tumor-promoting inflammation.

Naturally derived compounds, such as soy isoflavones, curcumin, apigenin, and wogonin, can therefore be used to negate pro-tumor inflammation and help bring forth the necessary antitumor cytotoxic capabilities (Pavese et al. 2010; Lee 2013; Dandawate et al. 2012). In this chapter we cover the development and consequences of aberrant inflammation and the important pathways commonly found in inflammation and consider mechanisms by which plant-derived compounds would modulate such inflammatory immune responses. We also aim to bring forth evidence that supports naturally derived compounds as a possible addition to conventional treatment.

12.2 An Introduction to Natural Compounds

Natural compounds have shown promising results both in vitro and in vivo studies as anti-tumorigenic agents, especially regarding their capacity to modulate an anti-inflammatory response. Various cellular pathways are targeted by these compounds, ranging from induction of pro-apoptotic pathways to providing antioxidant support within the stromal cells. Plant extracts provide readily accessible phytochemicals which aid in cancer treatment and prevention at a relatively inexpensive cost. Plant phytochemicals such as polyphenolic flavonoids and terpenoids have shown to be quite effective as anticancer agents (Thoppil and Bishayee 2011). Although a large number of natural compounds have been discovered as having potential anticancer

activity, the extent of this chapter will be geared towards compounds which directly or indirectly modulate the tumor-immune interaction. Most of the discussed plant-derived compounds/polyphenols are "anti-inflammatory" in nature. Therefore, it is plausible that they modulate the pro-tumor inflammatory response by affecting the stromal immune components as much as, if not more than, its direct effects on the cancer cells.

Many naturally-derived compounds lie under the classification of phytochemicals, a group of compounds that exhibit a wide range of beneficial biological activity. Phytochemicals can be subdivided into groups, depending on their origin and chemical composition. Their activity can range from directly promoting apoptosis, to providing vital antioxidant capabilities, to inhibiting the production of pro-inflammatory molecules (Zubair et al. 2017; Surh et al. 2001). Examples of phytochemical classes include anthocyanins, flavonoids, glycosides, terpenoids, and tannins. Phytochemicals found in soy, turmeric, and Scutellaria are of particular interest because of their immunomodulating capabilities. More specifically, active phytochemicals found in these extracts help inhibit pro-tumor inflammatory states. The active phytochemicals found in the extract from Scutellaria include apigenin, baicalin, oroxylin A, scutellarin, and wogonin, among many others (Hussain et al. 2016). The main compound in soy pertinent to this chapter includes the isoflavone genistein (Banerjee et al. 2008). From turmeric, the active compound we will focus on is curcumin. Each of these compounds exhibits immunomodulatory forms of action, with some compounds having overlapping mechanisms of modulating the immune system. These phytochemicals work to prevent the induction or expansion of immune-suppressing mechanisms or provide additional support to move the immune system towards antitumor, cytotoxic immune response.

12.3 Innate Immune Components of Anti- or Pro-tumor Inflammation

The innate immune system is composed of cells which include monocytes/macrophages, dendritic cells, granulocytes (neutrophils and basophils/mast cells), innate lymphoid cells, and natural killer (NK) cells. The innate immune system responds systematically in an attempt to rectify perceived danger or distress due to pathogen attack or tissue damage, respectively. Danger signals are received via different receptors including toll-like receptors (TLRs), NOD-like receptors (NLRs), RIG-I-like helicases (RLHs), or glycan receptors (Roach et al. 2005). TLR's primary role is to activate specific pathways by dimerization in response to the recognition of their respective ligands. These ligands are molecules called pathogen-associated molecular patterns (PAMPs) as well as damage-associated molecular patterns (DAMPs) (Charles and Janeway 2002; Garg et al. 2013; Lotze et al. 2007; Tang et al. 2012). An example of PAMP is LPS, a lipopolysaccharide found in a large majority of gram-negative bacterial cell walls. The stimulation of TLR4 by LPS transduces a signal which can proceed to promote a pro-inflammatory response.

DAMPs are important host cellular molecules which are released during injury, such as a necrotic event. Because of cancer's virulent nature, the stress due to overactivation of metabolic and catabolic pathways can result in the accumulation of reactive oxygen species, ROS. This can cause excessive oxidative stress pushing cells into apoptosis or oxidative burst, which in turn leads to the release of distress signals such as hypoxia inducible factor (HIF), heat-shock proteins (HSP), and high mobility group box 1 (HMGB1) (Oberley 2002; Reuter et al. 2010). DAMPs act as signals to alert the body of distress, allowing for a proper immune and repair response. Via the DAMP–TLR interaction, the innate immune system responds by producing pro-inflammatory cytokines such as Il-6 and tumor necrosis factor alpha (TNF-α) (Zhang and An 2007). In a normal immune response, pro-inflammatory molecules are regulated in such a way that allows for either activation or inactivation of pro-survival or pro-death pathways, dependent on intracellular conditions (Hehlgans and Pfeffer 2005).

After the release of DAMPs into circulation from necrotic events, an immune response is elicited by activation of cellular receptors on resident macrophages and neutrophils (Newton and Dixit 2012). Detection can also occur by patrolling NK cells (Wu 2003). This promotes the production and release of cytokines and chemokines that aid in the chemotaxis of other immune cells. In response, specific intracellular signal transduction pathways are activated, and depending on the ligand present different signal transduction pathways can induce a cytotoxic or inflammatory response (Zhang and An 2007; Lu et al. 2008; Wong et al. 2001).

Neutrophils, NK cells, and monocytes/macrophages form a front-line defense system to stop and prevent further damage from perceived harm. Immune surveillance provided by these innate immune cells also provides a mechanism to recognize and provide a cytotoxic response to emerging hyperplastic cells. NK cells are one of the first in line during the development of an active antitumor immune response. NK cells monitor for cellular abnormalities throughout the body to prevent the proliferation of hyperplastic cells. Several TLRs are also expressed on the NK cell's surface. Activation of these receptors via DAMPs from necrotic events allows for the secretion of interferon-gamma (IFNγ), a potent cytokine necessary in the activation of macrophages (Vivier et al. 2008; Mosser and Edwards 2008).

Macrophages perform fundamental housekeeping throughout the body, mainly by phagocytizing cellular remnants and debris. The role of housekeeper is essential in order to deal with the constant cell turnover and need to recycle any leftover cellular material. During times without threat, macrophages remain in an inactivated state; their morphology and capabilities tend to be focused solely on their housekeeping duties and perform these tasks without provocation. In comparison, an activated macrophage takes a more protective stance, focusing on phagocytizing pathogens, with the combined ability of antigen presentation. Activation only occurs once molecular signals have been received via danger signal receptors along with cytokines, such as IFNγ, secreted from either NK cells or helper T cells. Activation of macrophages can result in a M1 or M2 phenotype, each with distinct capabilities, with M1 leaning towards a more cytotoxic oriented response and M2 more oriented to a regulatory, wound-healing-type response. M1 and M2 macrophages tend to

coincide with whichever helper T-cell response has been elicited (Wang et al. 2014a). Noteable is the debate surrounding the simplistic nomenclature, as macrophage capabilities vary and lie on a spectrum not solely dependent on a Th1 or Th2 response (Martinez and Gordon 2014). IFNγ or TNF-α is an important cytokine needed to activate macrophages and helps to provoke either an antitumor or pro-inflammatory response, respectively (Mosser and Edwards 2008).

As tumorigenesis progresses, the tumor stroma can trick macrophages into providing support for a pro-tumor environment. Tumor-associated macrophages, or TAMs, are a result of advanced cancer and aid in anti-cytotoxic, pro-metastatic activities preventing the immune system from mounting a correct response against the progressing cancer (Cortez-Retamozo et al. 2012). Production of inflammatory molecules, angiogenic factors, and metalloproteases all result from TAM transforming from M1- into M2-type macrophages and this creates a stromal environment rife for tumor progression and metastasis. Major cytokines produced by TAMs include TGF-β and EGF, which can cause immunosuppression and support tumor cell extrication.

Neutrophils are the most abundant cells found in the human innate immune system and one of the shortest-lived with an average life span of well under 24 h. They are important mediators in the progression of inflammation, purveyors of both cytokines and reactive oxygen species (Kolaczkowska and Kubes 2013). Neutrophils are in constant circulation throughout the body and utilize cell-specific adhesion molecules and cytokines, such as IL-8, during activation. Activation is a multistep process which includes the priming of neutrophils by typically an inflammatory molecule, such as TNF-α. After priming, neutrophils are activated by stimulation of TLRs. Once activated, the life span of neutrophils dramatically increases to 1–3 days. Activated neutrophils perform a multitude of important tasks, including trafficking dendritic cells, promoting inflammation and phagocytosis, or providing a wound repair response (Mayadas et al. 2014).

Interleukin 8, or IL-8, or CXCL8 is a member of the CXC chemokine family and regarded as a pro-inflammatory cytokine that is heavily involved in the chemotaxis and extravasation of neutrophils (Bickel 1993). Production involves TNF-α activation of the NF-kB and Akt pathways. IL-8 can also cause degranulation of histamines in target tissues (Lacy 2006). IL-8 is an autocrine growth factor in certain cancers and can promote angiogenesis in several others, including both colon cancer and lung cancer. As a cytokine, IL-8 is an important mediator of mitogenic factors which promote cell survival and exacerbate inflammation. IL-8 works through G protein-coupled receptors called CXCR1 and CXCR2. Activation of these receptors has the capability of stimulating multiple pathways including PI3k/Akt, NF-kB, STAT3, and AP-1. Its proliferative and immune-modulating nature makes it a key component to target in attempts to prevent inflammation (Waugh and Wilson 2008).

Medicinal plant- or food-derived phytochemicals have been shown to modulate various components of tumor-associated innate immune components via various mechanisms. Research done by Peng et al. indicated that administration of Scutellaria extract in a dose-dependent manner lowered serum levels of IL-8 in mice bearing U14 cervical cancer (Peng 2014). The study did show a contradiction as

levels of TNF-α were elevated in a dose-dependent manner as well. Even so, the study displayed suppressed immune responses in the control group, while an enhanced immune response was observed in mice who received Scutellaria extract. The elevated levels of TNF-α may indicate the extract played a role in recruiting NK cells to combat the cancer (Pilaro et al. 1994). More research is needed to confirm this theory (Fridlender et al. 2009; Fridlender and Albelda 2012).

There is a conspicuous correlation between higher levels of expressed cell adhesion molecules and monocyte migration. To initiate chemotaxis from TANs and TAMs, they require IL-1β, IL-6, and CXCL8 (IL-8). Production of these molecules is often regulated by the Akt pathway and in many cancer cells the Akt pathway is constitutively active (Testa and Tsichlis 2005). Gong et al. reported that genistein, a key soy isoflavone, inhibits the Akt pathway in MDA-MB-231 breast cancer cells (Gong et al. 2003). Inhibition of this pathway prevents the production of cell adhesion molecules preventing the migration of TANs and TAMs and their capability to modulate the immune system and prevent inflammation. Our group has previously shown that a leaf extract of Scutellaria inhibits glioma growth in mouse models via inhibition of the Akt pathway (Parajuli et al. 2011).

TGF-β exerts robust pro-tumorigenic activities and plays a tremendous role in controlling the immune system. In general TGF-β inhibits cytotoxic responses from the immune system and blocks antitumor activities. The culmination of these effects on macrophages then promotes their activities to become pro-inflammatory. It stimulates T cells to become regulatory, immune-suppressing cells, also known as T regulatory cells. Enhanced Treg activity has been attributed to more advanced stages of cancer (Takeuchi and Nishikawa 2016). Li et al. displayed that genistein prevents RNA expression of TGF-β, therefore inhibiting all of TGF-β downstream effects (Li 2002).

12.4 The Important Roles of $CD4^+$ T-Helper and Treg Cells

Different pathways are activated in the immune system to help dictate whether a continued aggressive cytotoxic response is needed, or if the body should be preparing for a wound-healing response. Coordination of these responses is an important factor when dealing with a pathogen or an injury. There are dichotomous differences between these two response pathways and result in largely divergent actions. There needs to be a logical system the body can take to prevent potentially dangerous consequences due to an incorrect response. The body does not want to promote a healing environment when pathogens are still present. Orchestration for a proper response comes in part by means of a subset of T cells named T-helper cells, or Th cells.

Naïve helper T cells are involved in a process of differentiation that aids in the progression towards an effective adaptive immune response (Janeway 1989). There are large differences between effector Th1, Th2, and Th17 $CD4^+$ cells and each promotes a specific agenda which, under normal circumstances, is supposed to

reflect the nature of the pathogen (Kaiko et al. 2008). Each T-helper cell response has a profoundly different outcome and is evoked by specific cytokines and chemokines secreted by surrounding stromal cells. Aberrant helper T-cell differentiation is also known to play a role in multitude of autoimmune diseases (Charlton and Lafferty 1995; Lafaille 1998; Yuan Zhang et al. 2014).

$CD4^+$ Th1 cells are geared towards intercellular assault, such as viral invasion and cancer proliferation. Excess inflammation is not required for a proper immune response within the tumor environment; therefore, a Th1-mediated response is more advantageous in preventing tumorigenesis. Extracellular pathogens on the other hand require a response geared towards removing and expelling them from the body (Anthony et al. 2007). The consequences of a prolonged inflammation mediated by Th2 cells are explained later in this chapter.

$FoxP3^+$ regulatory T cells, or Treg cells, are an important part of the immune system originally geared to prevent autoimmune responses towards self-antigens. Their capability to suppress the immune system is far reaching, with mechanisms that inhibit T cells, B cells, macrophages, dendritic cells, and NK cells. Treg cells work through a few different methods of actions, with the capacity to produce cytokines (TGF-β and IL-10) and cell-surface molecules (CTLA-4) involved in promoting anergy and apoptosis in surrounding immune cells. TGF-β also plays a critical role in the expansion of Treg cell population in the tumor microenvironment (Takeuchi and Nishikawa 2016). We have reported that Scutellaria extract and its active constituent wogonin reduce the accumulation of $FoxP3^+$ Treg cells in animal models of glioma via inhibition of TGF-β signaling (Dandawate et al. 2012). Scutellaria extracts prevented the secretion of TGF-β from glioma cells while also inhibiting the generation/expansion of Treg cells via modulation of intracellular, SMAD-mediated TGF-β signaling (Dandawate et al. 2012).

In a study by Xu et al. Treg cells were shown to be downregulated by curcumin via inhibition of the FoxP3 gene transcription and subsequently converted into Th1 cells. This prevented the immunosuppressive effects of Treg cells while also promoting a cytotoxic immune response in patients with advanced colon cancer (Xu et al. 2017). Kan et al. displayed that Scutellaria extract has additional Treg-modulating activities in H22 hematoma-bearing mice. This was observed via downregulation of the cytokines IL-17, TGF-β, and IL-10, while the levels of Th1 cytokines IL-2 and IL-12p70 were elevated. Furthermore, tumor-infiltrating Th17 and Treg cells were also inhibited after treatment with Scutellaria extract (Kan et al. 2017). As a noteworthy point, there is a lack of evidence that supports the definitive upregulation of Th1 cells. No tests were performed to show the levels of Th1 cells before or after administration, only measurements of relevant cytokines.

Clinical studies have also exhibited promising results in the ability to modulate $FoxP3^+$ Treg cells. A study by Lesinski et al. showed that consumption of soy isoflavone-fortified bread by 32 men with prostate cancer displayed a large decrease in Treg cells after 56 days (Lesinski et al. 2015). This provides key clinical evidence supporting claims that digestible soy isoflavone intake has immune-modulating capabilities.

12.5 TNF-α and NF-κB

Immune cells are greatly influenced by the cytokine TNF-α. TNF-α receptors, or TNFR, come in two types, I and II, with type II primarily found on immune cells. Activation of these receptors is a key step in the inflammatory process (Parameswaran and Patial 2010). After induction of the TNF-α-TNFR complex, a key downstream effector, nuclear factor kappa-light-chain enhancer of activated B cells (NF-κB), can be activated (Hayden 2004). Many of the inflammatory properties of immune and stromal cells are elicited through activation of NF-κB (Sabroe et al. 2008; Mantovani et al. 2008; Hoesel and Schmid 2013). Natural compounds have proven to be great inhibitors of NF-κB, therefore preventing the inflammatory effects of TNF-α.

TNF-α can act in paradoxical roles within the cell depending on the microenvironment. TNF-α is primarily secreted by either activated macrophages, or effector T cells, but can also be secreted by other surrounding stromal cells (Parameswaran and Patial 2010). Under normal homeostatic conditions, TNF-α works as a pro-survival molecule (MacEwan 2002). TNF-α can mediate apoptosis but only once both PI3K/Akt and NF-κB pathways have been inhibited (Rath 1999). Because TNF-α is such a potent cytokine and activator of many inflammatory responses, its downstream effector molecules provide possible targets to prevent inflammation while also inducing apoptosis in cancer. In both cancer and some autoimmune diseases, TNF-α is produced in excess, and has already been used as a target to inhibit the initiation and progression of inflammation (Bradley 2008).

NF-κB is an essential transcription factor needed for initiating inflammation in cancer (Hoesel and Schmid 2013; Fan et al. 2013). Its activation causes a snowball effect, with the activation of multiple cellular processes, mostly geared towards cell survival and production of pro-inflammatory molecules such as LOX-5 and COX-2. NF-κB can also cause the production and activation of inducible nitric oxide synthase (iNOS), a producer of powerful reactive nitrogen species. Tumor-related inflammation and immune suppression rely on the constitutive activity of NF-κB and its downstream effectors.

Curcumin has been shown to inhibit NF-κB and prevent the actions of its downstream effectors (Bharti et al. 2003). Curcumin directly binds to IκBα and inhibits the necessary phosphorylation and cleavage of said complex to activate NF-κB (Singh and Aggarwal 1995). Without these steps, NF-κB cannot translocate into the nucleus and start the initiation of transcription. Curcumin has also been shown to directly attach to COX-2, a molecule widely known for its role in promoting inflammation (Lee 2013). Furthermore, iNOS is also a target for curcumin, which further helps inhibit inflammation (Brouet and Ohshima 1995).

Genistein also works by regulating and inhibiting NF-κB (Zhou 2014). Genistein has been shown to prevent the translocation of NF-κB after exposure to TNF-α (Davis et al. 1999). The interpreted explanation was inhibition of phosphorylation of the IκBα complex.

Scutellaria extract has also been shown to inhibit NF-κB activation. NF-κB is activated through multiple mechanisms. One mode of activation occurs when the precursor complex IKK is exposed to excess reactive oxygen species. Scutellaria extract, which contains the active antioxidants wogonin, oroxylin A, baicalin, and baicalin, can scavenge reactive oxygen and nitrogen species and inhibit IKK and NF-κB activation (Hussain et al. 2016). In glutathione-depleted cells, curcumin has also shown signs of an inverse mechanism of inhibiting NF-κB. This occurs by excess production of ROS that then leads to degradation of IKK instead of ROS activation (Sandur et al. 2007).

As previously stated, activation of NF-κB results in a wide range of outcomes and its inhibition causes widespread intracellular and extracellular effects. Curcumin also prevents TNF-α-mediated activation of NF-κB by interaction with IκBα and prevents nuclear translocation of NF-κB (Bharti et al. 2003).

Inhibition of NF-κB can allow for apoptosis of cells responsible for perpetuating inflammation. The pro-apoptotic effects of curcumin have been attributed to the inhibition of PI3k/Akt pathway, preventing the necessary phosphorylation of Akt, which is needed to continue signal transduction. This causes inhibition of downstream effectors including two major anti-apoptotic proteins BCL-2 and BCL-XL. Inhibition of this pathway also helps promote activation of caspase-3, a key regulatory molecule in the apoptotic pathway (Lee 2013).

12.6 Natural Compounds, a Plausible Alternative

Naturally derived compounds have been used for centuries to combat inflammation. For instance, written history has documented the use of willow bark, which contains acetylsalicylic acid, the active ingredient in aspirin, as a form of treatment for various ailments dating back to the Roman empire (Norn 2009). It should then be noted that some of the most important anticancer drugs, such as vinca alkaloids, are naturally derived (Moudi et al. 2013). Anticancer and immune-modulatory activities of select phytochemicals are summarized in Table 12.1.

Soy isoflavones have exhibited great potential as immune-modulating compounds (Banerjee et al. 2008; Abernathy et al. 2015, 2017). Genistein has emerged as a multifaceted compound, showing signs as a potential form of adjuvant cancer therapy with possible applications outside of cancer treatment, including treatment for Alzheimer's and atherosclerosis, both via inhibition of inflammation (Zhou 2014; Wang et al. 2008). Although soy products have been under debate over the efficacy and safety of use in certain types of cancer, specifically breast and prostate cancer, research has leaned towards soy possessing beneficial effects rather than the commonly believed negative impact when consumed or used therapeutically (Davis et al. 1999). Soy products are known to have weak estrogenic effects. In certain breast cancer, specifically ER^+ breast cancer, growth is considered to be estrogen dependent. Logically there has been speculation as to whether soy and possible

Table 12.1 Naturally derived compounds: functions and molecular mechanism

Origin of compound	Compound	Function	Molecular mechanism	References
Turmeric	Curcumin	Inhibits production of pro-inflammatory molecules	Direct inhibition of NF-κB, COX-2, iNOS	Lee (2013); Brouet and Ohshima (1995)
		Pro-apoptotic	Inhibition of the PI3k/Akt pathway, inhibition of NF-κB	Lee (2013); Singh and Aggarwal (1995)
		Inhibits TNF-α stimulation	Attachment to IκBα	Bharti et al. (2003)
		Upregulation of Th1 cells	Prevention of FoxP3 expression	Xu et al. (2017)
Soy	Genistein	Inhibition of Treg cells	Downregulation of multiple pro-inflammatory cytokines	Lesinski et al. (2015)
		Inhibits production of pro-inflammatory molecules	Inhibition of NF-κB	Zhou (2014)
		Inhibits TNF-α stimulation	Prevention of translocation of NF-κB	Davis et al. (1999)
		Inhibits TGF-β production	Prevention of RNA transcription of TGF-β	Li (2002)
Scutellaria	Apigenin	Inhibits production of pro-inflammatory molecules	Inhibition of COX-2, iNOS and NF-κB (p65)	Choi et al. (2004); Wang et al. (2014b); Liang et al. (1999); Patil et al. (2016)
	Wogonin	Inhibition of Treg cells	Inhibition of TGF-β	Dandawate et al. (2012)
		Inhibition of pro-inflammatory pathways	Inhibition of IKK and NF-κB activation	Hussain et al. (2016)
	Oroxylin A	Inhibits release of IL-6, IL-1b	Inhibition of Jak/STAT pathway	Hussain et al. (2016)
	Baicalin	Inhibition of pro-inflammatory pathways	Inhibition of TLR2 formation, inhibition of Th17 cell	Hussain et al. (2016)
	Scutellarin	Inhibition of pro-inflammatory pathways	Inhibition of TLR4 formation	Hussain et al. (2016)
	Extract (nonspecific)	Inhibition of pro-inflammatory pathways	Inhibition of Akt, GSK-3α/β and NF-κB pathways	Parajuli et al. (2011)
		Inhibition of Treg cells	Inhibition of production of IL-17, TGF-β, and IL-10	Kan et al. (2017)

estrogenic effects could be deleterious in such cancers, the rationale being that it could promote further growth. Yet even after multiple clinical studies, a definitive decision on possible negative effects due to soy intake has resulted in inconclusive evidence. Rather, more current studies have shown evidence that soy products may have the capacity to be competitive inhibitors of estrogen in ER^+ breast cancers and therefore aid in the prevention of tumor growth and progression (Messina and Badger 2017; Kwon 2014).

Turmeric has an extensive and long history of being used as an anti-inflammatory agent (Prasad and Aggarwal 2011). Curcumin, the active compound in turmeric, has shown great versatility in controlling and preventing inflammation. One very positive aspect of curcumin is its low toxicity even at very high doses (Gota et al. 2010). This versatility of curcumin comes in part due to its structural diversity. The tautomerization between a keto-enol form is dependent on the surrounding pH and can perform different tasks depending on the current form curcumin is in (Lee 2013). Many of the benefits from curcumin stem from the inhibition of NF-κB and the Akt pathways, allowing for the prevention of pro-inflammatory cytokines and potential apoptosis of cells which produce them.

Most of the active flavonoids in Scutellaria extract display potent antioxidant capabilities. Some key targets for each of these include the following: Baicalin inhibits Th17 cell maturation, lowering pro-inflammatory cytokines and positive feedback loop that perpetuates inflammation. Baicalin also prevents the expression of TLR2s, a member of the TLR family known to promote the production of TNF-α once activated. Scutellarin inhibits TLR4 expression, a receptor associated with perpetuating low-grade inflammation. Oroxylin A functions through the JAK/STAT pathway, unlike other active compounds in Scutellaria. It does so by inhibiting the phosphorylation of STAT in the JAK/STAT pathway, because of this, cytokines IL-1β and IL-6 cannot be released, preventing the activation of other inflammatory genes in the surrounding environment (Hussain et al. 2016).

Another compound with characteristics as a potential immune modulator is the flavonoid apigenin. Found in a wide variety of fruits, vegetables, and other plant-derived products, e.g., chamomile tea, parsley, oranges, and Scutellaria, apigenin has been found to be nontoxic at levels which correlate to normal human consumption (Janssen et al. 1998; Fernandez de Simon et al. 1992; Lemberkovics 1998). Apigenin can be found in detectable levels in urine samples after administration of a 2-gram bolus of parsley, suggesting a relatively good bioavailability with a calculated half-life of 12 h in human subjects (Nielsen et al. 2007). Apigenin can inhibit both COX-2 and iNOS, as well as TNF-α-induced NF-κB activity by inhibiting p65-DNA complexes needed for transcription of important pro-inflammatory molecules (Choi et al. 2004; Wang et al. 2014b; Liang et al. 1999; Patil et al. 2016). Apigenin also directly represses the activation of the LPS-induced inflammatory response in macrophages. Zhang et al. have reported a sharp, dose-dependent, downregulation of NF-κB activity and production of the inflammatory cytokines IL-1β, IL-6, IL-12, and CCL5, as well as the cell adhesion molecules ICAM and VCAM (Zhang et al. 2014). This is done via downregulation of both the transcription of pro-inflammatory genes and inhibiting the production of cytokines central to promoting an inflammatory response.

There is promising evidence for naturally derived adjuvant therapy in the treatment of cancer. Because many cancers share similarities in the activation of onco genes and repression of tumor-suppressor genes, especially those involved in mediating inflammation, this creates a consistent target that naturally derived compound can inhibit. Thus, natural compounds can potentially provide a multifaceted nontoxic approach towards treating cancer without deleterious side effects.

12.7 Conclusion

Plants have proven time and again to have great versatility in producing multifaceted compounds for use as instruments for their own survival. This versatility allows for such compounds to be utilized elsewhere as a potential modulator of the human inflammatory immune responses. Many of these anti-inflammatory compounds contain chemical structures which allow for multiple modes of interaction with minimal side effects to the host at therapeutic dosage. Proper application of these compounds and their distinct properties should be considered as potential novel therapeutic agents.

The immune response to cancer varies throughout the progression of cancer. During the initial stages, it provides a cytotoxic response, aimed at targeting aberrant cells proliferating rapidly. The formation of a tumor provides a hypoxic environment which activates innate immune cells, including NK cells, starting the cascade of events which results in acute inflammation and activation of an adaptive cellular and humoral immune responses. However, as time progresses, and inflammation becomes a chronic situation, it can create an environment rife for tumorigenesis. This transition into a chronic, inflammatory, pro-tumor, Th2-mediated, TGF-β-producing environment results in a suppressed immune response and allows for production of pro-tumor cytokines and growth factors which help in the progression of tumorigenesis. In progressing cancer, the immune response can be polarized and eventually used against the body, perpetuated through continued immunosuppression via the development of Treg cells, TAMs, and TANs.

Immunotherapy can be a robust tool in the fight against cancer. It can provide the functionality needed to stop tumor progression without affecting surrounding normal cells. Immune-regulatory activities mediated by TGF-β, Treg, and TAM are great impediments to successful immunotherapy. By administering naturally derived compounds with immune-modulatory capabilities, we can not only inhibit pro-tumor inflammation but also potentially redeploy an antitumor, cytotoxic immune response. Phytochemicals found in turmeric, soy, and Scutellaria have shown profound effects on attenuating and modulating inflammation. Further research could pave ways toward combining these natural compounds with various forms of immunotherapeutic strategies against cancer.

To suitably implement these natural compounds as immune-modulating agents during tumorigenesis, further research should be done to fully understand the range of possibilities and capabilities each of these compounds has. Contemporary modes

of cancer therapeutics need nontoxic forms of adjuvant immunomodulatory agents. By properly applying these naturally derived compounds, a mediator that provides multiple modes of action can be used to significantly improve the clinical outcome of conventional therapies.

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