Chapter 4
Cancer Therapy-Induced Inflammation and Its Consequences

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Abstract The inflammatory process often modifies the natural history of cancers. There is broad evidence that chronic inflammatory responses, associated with, e.g., persistent viral or bacterial infections, promote carcinogenesis. Cancer treatment is also associated with an inflammatory process that may either induce an antitumor immune response or, conversely, favor tumor recurrence. Here, we will revise the major aspects of therapy-induced inflammation and its consequences for tumor recurrence or repopulation, emphasizing how the mode of tumor cell death elicits an antitumor response, the key elements associated with the clearance of dead cells within the tumor microenvironment and the unleashing of an innate tissue regenerative response, dependent on lipid mediators such as prostaglandin E2 and the platelet activation factor (PAF), that favor tumor regrowth. Therapy-induced inflammation may offer a window of opportunity for combination therapies that increase the effectiveness of conventional cancer treatment modalities. Nanobiotechnology offers versatile platforms for anti-inflammatory interventions. Here we also discuss RNA-based approaches in the nanoscale, which would allow targeted interventions of pro-tumoral inflammatory milieu assembled in the course of therapeutic regimens in order to avoid the emergence of treatment-resistant cancer cells that ultimately repopulate the tumor mass.

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D. Ribeiro de Araujo, M. Carneiro-Ramos (eds.), *Biotechnology Applied to Inflammatory Diseases*, Interdisciplinary Biotechnological Advances,
https://doi.org/10.1007/978-981-19-8342-9_4

Keywords Inflammation · Cancer treatment · Chemotherapy · Radiotherapy · Immunotherapy · Tumor repopulation

4.1 How Cancer Therapy Induces Inflammation?

4.1.1 The Role of Cell Death

The main goal of most cancer therapies is to induce cancer cell death, in spite of the mechanisms of the distinct anticancer agents. Many cancer therapies are very effective in reducing the number of cancer cells by destroying these cells; however, the main challenge of these therapies is that they are not able to eliminate all cancer cells and residual resistant cells can proliferate and originate tumor reestablishment. Here, we will focus on the role of inflammation in cancer therapy resistance and we highlight the cell death process as a linker of these phenomena.

It is a consensus that the presence of microbes in injuries is a potent inducer of inflammation; however, sterile injury can also stimulate inflammation. Accumulated literature of more than 150 years after the first association between tissue injury and cancer made by Virchow reveals that inflammation is a crucial link between tissue injury and cancer. It is now well-accepted that tissue injury generates cell death that activates cytokine secretion by inflammatory cells to mediate wound healing. If inflammation gets chronic and is combined with carcinogen exposure, it can result in malignant transformation (Kuraishy et al. 2011; Fishbein et al. 2021). In this context, it is interesting to note that cancer therapies also result in cell death along with inflammation and can be viewed as a collateral effect stimulus for the survival and proliferation of residual cells. Thus, cell death-induced inflammation is linked to either tumorigenesis or cancer therapy resistance.

In 1994 Polly Matzinger introduced the "danger theory," which postulates that the immune system activity is not based on distinguishing self from non-self, but rather from dangerous or not stimulus (Matzinger 1994). Considering that cells often die as a consequence of an infection, dead cells can be recognized as danger signals by the immune system and trigger an inflammatory response in order to protect the host from a potential danger. However, not all dying cells induce inflammation, the way a cell dies dictates if an immune response will be initiated or not. According to Matzinger's argument, inflammation is induced by necrosis because this type of cell death is involved in cellular processes potentially dangerous to the host, such as infection, whereas apoptosis is associated with physiological processes. It has been assumed for a long time that the immune system triggers a strong inflammatory response upon cell membrane rupture during necrosis and in contrast, apoptosis was considered to be a silent cell death process. However, accumulating knowledge about cell death mechanisms revealed that there are programmed forms of necrosis (necroptosis, NETosis, and pyroptosis) that also induce inflammation. Moreover, it is now well-accepted that the concept of apoptosis as a noninflammatory process is an oversimplification.

Apoptosis is a silent process because at least initially, apoptotic cells maintain their plasma membrane integrity and are cleared by professional phagocytes [macrophages and dendritic cells (DC)]. Apoptosis can also be a tolerogenic process by preventing the release of anti-inflammatory cytokines [e.g., interleukin10 (IL-10) (Chung et al. 2006)] and transforming growth factor-β (TGF-β) (Huynh et al. 2002) by macrophages, suppressing DCs activation through decreasing IL-12 (Stuart et al. 2002) or attenuating type I interferon signaling by TAM receptor engagement (Lemke and Rothlin 2008). Interestingly, it has been demonstrated that a slow clearance of apoptotic bodies can lead to secondary necrosis, resulting in cell membrane permeabilization, release of pro-inflammatory contents, and stimulating the immune system (Majno and Joris 1995). Thus, the efficiency of apoptotic cell clearance is a key factor in determining between silent and inflammatory apoptosis. As mentioned above, the strategies to treat cancer are diverse and the same is valid for the cell death mechanisms elicited by them; however, all signaling pathways leading from cancer therapy-induced cell death converge to inflammation.

4.1.2 How Cell Death Signals in Inflammation and Immunity?

From a mechanistic view, how do dead cells induce inflammation? As aforementioned, how a cell dies matters to understand how they induce inflammation or immunity. The most predominant cell death process elicited by the majority of chemotherapeutic drugs and radiotherapy is apoptosis. When a cell dies through apoptosis, it immediately releases soluble signals, which are classified into (1) "find-me signals," which attract phagocytes, mainly macrophages; and (2) "eat-me signals," which promote their engulfment (efferocytosis). An effective clearance of dying cells is crucial to avoid the release of potential autoantigens; however, impaired clearance of apoptotic cells is often observed after anticancer treatment. One evidence of this is that neutropenia is a common consequence of cancer treatment, which limits the tolerable dose of chemotherapy (Crawford et al. 2004). Additionally, the efferocytosis activity of the remaining phagocytes can be inhibited by some FDA-approved chemotherapeutic agents, including tamoxifen, sorafenib, bevacizumab, vinblastine, and vincristine (Green et al. 2016). Additionally, it has been shown that upon epirubicin/docetaxel combination therapy, HMGB1 circulating levels are increased in breast cancer patients (Arnold et al. 2013). Considering that both drugs cause neutropenia and HMGB1 is released during secondary necrosis, this piece of evidence supports the notion that cytostatic therapies not only induce apoptosis but can also trigger secondary necrosis.

A major characteristic of secondary, primary, and regulated necrosis is plasma membrane rupture accompanied by the release of intracellular molecules that become damage-associated molecular pattern molecules (DAMPs). The number of intracellular compounds from dying cells that are able to trigger inflammation is

unknown and the list of DAMPs is still growing. The nature of DAMPs is diverse and they can be prevenient from almost any cellular compartment: cytosol (e.g., uric acid, heat shock proteins, ATP), mitochondria (e.g., mtDNA, formyl peptides, ATP), nucleus (e.g., HMGB1, histones, DNA), plasma membrane (e.g., syndecans, glypicans), and endoplasmic reticulum (e.g., calreticulin) (Bianchi 2007). Following radiotherapy or treatment with some chemotherapeutic agents, tumor cells can release DAMPs which bind to different receptors (TLR2, TLR4, TLR9, and RAGE) present on the membrane of innate immune cells. As a consequence of this recognition, DC is activated and triggers engulfment of dying tumor cells, followed by tumor antigen processing and presentation to T cells. Ultimately, CD4+ and CD8+ T cells and natural killer (NK) cells are recruited to execute their antitumoral response (Hernandez et al. 2016).

This beneficial antitumor role of DAMPs has been shown in experimental models. Apoptotic cancer cells generated by ex vivo exposure to certain anticancer agents (e.g., anthracyclines, oxaliplatin, and ionizing irradiation), mediate an "anticancer vaccine effect," in the absence of any adjuvants or immunostimulatory substances, when implanted subcutaneously into immunocompetent mice (Casares et al. 2005; Obeid et al. 2007). Interestingly, subcutaneous implantation of secondary necrotic cells, originated by doxorubicin treatment, into syngeneic immunocompetent mice induces an antitumoral response mediated by adaptive immune system. In contrast, primary necrotic cells did not induce a protective immune response (Casares et al. 2005). Thus, the final therapeutic outcome of antitumor therapies is cytotoxic effects with tumor burden reduction, but in parallel, they can subsequently prime the immune system and promote anti- or pro-tumoral responses.

It was long believed that DAMPs were exclusively released from necrotic cells; however, it is now well-accepted that specific forms of programmed cell death can also trigger DAMP release, leading to the process of "immunogenic cell death" (ICD) defined as a form of regulated cell death (RCD) that is sufficient to activate an adaptive immune response in immunocompetent syngeneic hosts (Galluzzi et al. 2020). ICD can be induced by different anticancer treatments such as chemotherapeutic drugs [including anthracyclines (doxorubicin and idarubicin), platinum-based compounds (oxaliplatin), cyclophosphamide, mitoxantrone, and dipeptides (bortezomib)], γ-irradiation and photodynamic therapy (PDT) (Krysko et al. 2012). It is worth noting that not all cytotoxic agents can drive ICD, despite their similar RCD-inducing capability. The reason for this divergence relies on the fact that ICD induction depends on specific intracellular responses driven by the initiating stressor such as reactive oxygen species (ROS)-based endoplasmic reticulum (ER) stress (Garg et al. 2012).

However, DAMPs may also have a key role in cancer progression and resistance to anticancer treatments. DAMPs mediate tumor progression via distinct mechanisms, for example, HMGB1 may contribute to immunosuppression, angiogenesis, tumor cell proliferation, and inflammation (Hernandez et al. 2016). Several studies have underlined the effect of DAMPs on the resistance of tumor cells to different anticancer treatments. Chemotherapy-induced release of HMGB1 results in docetaxel resistance in prostate cancer cells (Zhou et al. 2015) and favors the

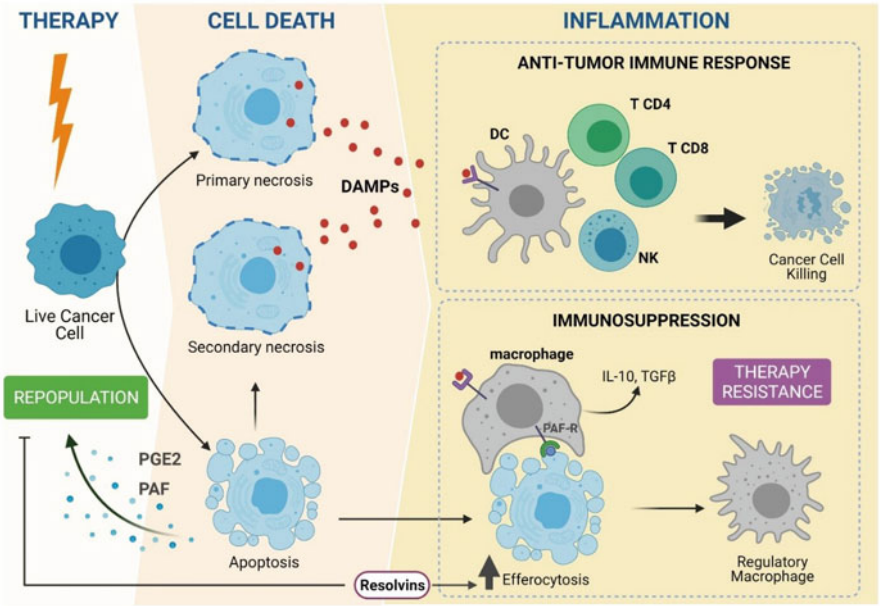

Fig. 4.1 Therapy-induced inflammation, friend or foe? Dying cells (necrosis) generated by anticancer therapy release damage-associated molecular patterns (DAMPs). DAMPs activate dendritic cells and increase tumor antigen presentation, resulting in an antitumor response that improves therapeutic outcome. Dead cells also recruit macrophages to execute their clearance (efferocytosis) and concomitantly it can polarize them toward a regulatory phenotype in a PAF-R-dependent manner, contributing to immunosuppression and rendering remnant cancer cells resistant to subsequent rounds of therapy. Dying cells also secrete lipid mediators, such as PGE2 and PAF, that can favor survival and proliferation of remnant cancer cells leading to tumor repopulation. Balance of this anti- and pro-tumoral consequences mediated by inflammation after therapy dictates the final therapeutic outcome (the figure was created using Biorender, biorender.com)

regrowth of remnant colon cancer cells after doxorubicin treatment (Luo et al. 2013). Additionally, released ATP can be hydrolyzed to adenosine, which has immunosuppressive activity and can promote a tumoral microenvironment that is associated with a reduction of antitumor immune responses efficacy (Ohta et al. 2006). Thus, while there is evidence that therapy-induced inflammation improves the therapeutic outcome by increasing tumor antigens presentation and consequent antitumor immune responses, there is also evidence that therapy-induced inflammation may promote tumor progression and favor therapy resistance. The ultimate response to anticancer therapy is dictated by the balance between anti- and pro-inflammatory mediators produced upon treatment, within a given dynamic immune landscape, which characterizes the tumor microenvironment (Fig. 4.1).

4.1.3 *Cytokines, Driving Mediators of Dying Cell-Induced Inflammatory Response*

Therapy-induced cell death stimuli trigger the release of DAMPs. DAMP-activated innate immune cells induce cytokines production, that are key mediators of inflammation (Fig. 4.2). The pivotal role of cytokines was initially considered as mediators of immune cell migration to the site of inflammation. Currently, we appreciate that these cytokines are also involved in tumor growth, progression, and therapy resistance (Chow and Luster 2014). Several studies have underlined the effect of cytokine production after anticancer treatments. Numerous in vitro and in vivo studies have shown evidence of changes in pro-inflammatory cytokine levels produced by a variety of cancer cells after administration of chemotherapy drugs (e.g., cisplatin, paclitaxel, 5-fluorouracil, and doxorubicin). We listed some of these findings in Table 4.1 to illustrate the diversity of pro-inflammatory cytokines generated by anticancer therapies. It has also been observed that inhibiting drug-induced cytokine signaling promotes the sensitivity of cancer cells to anticancer drugs. These studies suggest that the inflammatory cytokines released by tumor cells upon chemotherapy are implicated in mediating both resistance to cancer treatment. How do drug-induced cytokines alter tumor cell sensitivity to chemotherapy? One mechanism is altering pathways associated with apoptosis. Accordingly, the administration of recombinant human IL-8 to prostate cancer cells resulted in an increased expression of c-FLIP, an endogenous caspase-8 inhibitor (Wilson et al. 2008). Additionally, Sharma et al. (2013)) also demonstrated inhibition of spontaneous lung metastasis in

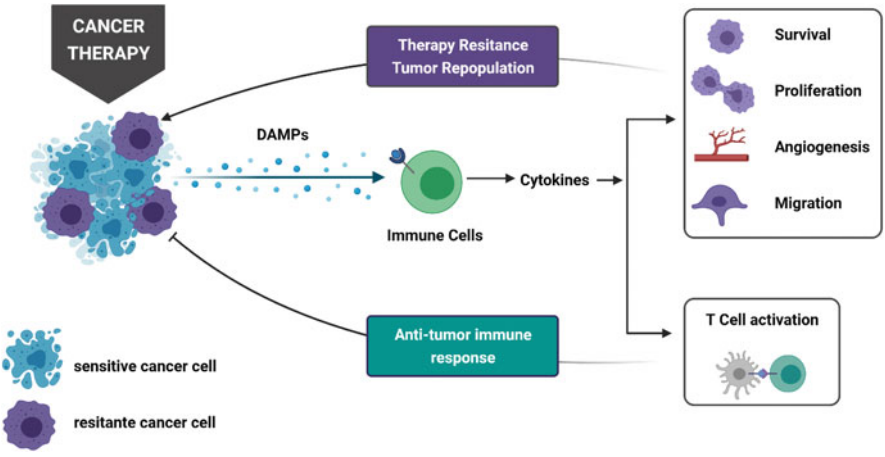

Fig. 4.2 Role of cytokines in therapy-induced inflammation. Following therapy, DAMPs generated by dying cancer cells activate cytokine-producing inflammatory cells. Cytokines bind to cognate receptors present in immune cells stimulating an adaptive antitumor immunity. Cytokines can also target residual cancer cells and induce pro-tumoral supportive phenotypes, such as cell survival, proliferation, angiogenesis, and migration, that promote therapy resistance and culminate in tumor repopulation (the figure was created using Biorender, biorender.com)

Table 4.1 Cytokine production upon anticancer therapy

Therapy	Cytokine	Cancer cell	References
Surgical resection	IL-1, TNF-α, IL-6	–	Desborough (2000)
5-Fluorouracil	IL-6, G-CSF, IL-1β	Head and neck squamous cell cancer	Reers et al. (2013)
Taxane	TNF-α	Breast and ovarian	Sprowl et al. (2012)
Cisplatin and paclitaxel	IL-8	Ovarian	Wang et al. (2011)
Oxaliplatin	CXCL8 and CXCL1	Prostate	Waugh and Wilson (2008)
Paclitaxel and doxorubicin	CXXL1	Breast	Sharma et al. (2013)
Irradiation	IL-6, -10, and TNFR1	Non-small cell lung cancer	Wang et al. (2010)
Irradiation	IL-6 and IL-8	Glioblastoma	Pasi et al. (2010)
Irradiation	IL-6 and IL-8	Human oral carcinoma cells	Tamatani et al. (2004)
Irradiation	IL-1, IL-6, and GM-CSF	Human lung cancer	Zhang et al. (1994)
Chemo-radiation	IL-6	Head and neck	Wang et al. (2010)

animals bearing CXCR2 knockdown tumors treated with paclitaxel. Chemokines can promote tumor cell migration as they act as attractant molecules, favoring the metastatic process. Indeed, several studies have underlined the effect of cytokines on promoting metastasis, as reviewed in Tanaka et al. (2005)). Considering that metastasis and chemoresistance in cancer are linked phenomena, cytokines production by tumor cells in response to chemotherapy are associated with the metastatic phenotype. Importantly, the role of cytokines in the tumor *milieu* goes much beyond their role as a chemoattractant, encompassing all tumor development steps, including tumor growth, angiogenesis, metastasis, and immune evasion, through immunoediting [reviewed in Raman et al. 2007 and Vyas et al. 2014].

Thus, tumor-promoting cytokines act in an autocrine or paracrine manner. Chemokines promote tumor growth by directly inducing cancer cell proliferation and migration, and indirectly by signaling to tumor stromal cells such as endothelial and immune cells favoring angiogenesis and immune evasion, respectively. CXCL8 is one of the cytokines produced by tumor cells that have both autocrine and paracrine pro-tumoral effects. This notion is supported by the evidence that IL-8-secreting prostate cancer cells were more resistant to docetaxel treatment and displayed increased vascular endothelial growth factor production along with increased microvessel density and abnormal tumor vasculature when compared with their vector-transfected control counterparts (Araki et al. 2007). In addition, IL-8 can signal for immune cell recruitment that contributes to cancer immune evasion. Tumor-derived IL-8 induces chemotactic recruitment of myeloid-derived suppressor cells (MDSC) (Alfaro et al. 2016) and DCs (Alfaro et al. 2011).

Interestingly, tumors producing IL-8 retain DCs and avoid their migration toward draining lymph nodes (Feijoó et al. 2005).

Not only tumor cells respond to chemotherapy-secreting cytokines, but also tumor stromal components, such as cancer-associated fibroblasts (CAFs) (Toste et al. 2016). It has been reported that gemcitabine treatment of CAFs induce upregulation of multiple inflammatory cytokines, including IL-8, that contribute to tumor-supportive phenotypes such as cell viability, migration, and invasion. Moreover, the inhibition of these cytokines attenuated these tumor-supportive functions. Considering all pro-tumoral roles of cytokines produced upon chemotherapy, they became a potential target for combined therapy. Indeed, in vivo studies have demonstrated that the specific inhibitor of CXCR4 receptor, AMD3100, sensitizes prostate cancer cells to docetaxel chemotherapy (Domanska et al. 2012). CXCR4 is the most common chemokine receptor expressed in most cancers and its ligand, CXCL12, is highly expressed on tumor stromal cells, mainly at the sites of tumor metastases and it is involved in homing of the tumors to different organs. Several in vitro and in vivo studies have demonstrated that the tumor-stroma interaction mediated by CXCR4/CXCL12 axis stimulates proliferation and migration of CXCR4-expressing cancer cells and is thought to protect them from cytotoxic chemotherapy [reviewed in Chow and Luster 2014]. Actually, the chemokine receptor inhibitor (CXCR4 antagonist AMD3100) is approved for the treatment of hematological malignancies (Mollica Poeta et al. 2019).

Not surprisingly, in vitro and in vivo studies have also demonstrated that radiotherapy induces an immediate inflammatory response with rapidly increased expression of many other inflammation-related cytokine genes (Hong et al. 1995; Schaue et al. 2012). Some examples of radiation-induced cytokine production are listed in Table 4.1. The general idea is that immediately after irradiation many cytokine cascades are activated sequentially, perpetuating an elevated cytokine production following irradiation. Fibrosis, a common late effect of radiotherapy, illustrates a consequence of this continuous cytokine response. Irradiation induced-cytokines unleash a persistent collagen production until apparent late effects of pathological fibrosis (Rubin et al. 1995). The cytokine cascade modifies the severity of the side effects observed post-irradiation. However, the biological implications of radiation-induced cytokine production go beyond its contribution to late radiation side effects, as cytokines can alter the primary tumor radiosensitivity. For example, IL-6 expression was positively linked with radiation resistance and IL-6 inhibition enhanced the radiation sensitivity of prostate cancer (Wu et al. 2013).

How irradiation-induced cytokines can modulate radiotherapy response? In mammalian cells, IR activates many pro-survival pathways that converge to transient activation of few transcription factors (TFs), including nuclear factor kappa B (NF-κB) and signal transducers and activators of transcription (STATs). IR induces a transient activation of NF-κB that is sufficient to produce multiple radioresistance signals, mainly by modulating anti-apoptotic pathways [reviewed in Magné et al. 2006]. The prevention of apoptosis, together with cell cycle arrest mediated by NF-κB activation after irradiation, favors a first moment DNA repair. However, sustained activation of NF-κB can allow the escape of radiation-induced DNA

damage cells from apoptosis (Jung et al. 1995). The central role of NF-κB regulation of radiation sensitivity and apoptosis after IR exposure was supported by the observation that cells from patients with ataxia–telangiectasia (AT) are hypersensitive to ionizing radiation but at the same time are defective in activating NF-κB and restoration of NF-kappa B regulation in these patients corrects the radiation sensitivity with a reduction of IR-induced apoptosis (Jung et al. 1995). In addition to apoptosis suppression, NF-κB activation regulates the transcription of a myriad of genes regulating immunity, proliferation, invasion, and angiogenesis, which favor radiotherapy resistance. Therefore, pharmacological inhibition of NF-κB would be a very interesting strategy to enhance tumor radiosensitivity. Indeed, compounds that suppress NF-κB activation, such as indomethacin and curcumin, enhanced radiation-induced apoptosis of Hela and prostate PC-3 cancer cells, respectively (Bradbury et al. 2001). Activation of the Jak-STAT pathway plays a significant role in radioresistance in different tumor models. Studies show that STAT3 mediates radioresistance of human squamous cell carcinoma (Bonner et al. 2009), prostate (Skvortsova et al. 2008), and breast cancer cells (Kim et al. 2006). Another member of the STAT family, STAT1, is also involved in renal cell carcinoma radioresistance (Hui et al. 2009). Targeting of STATs might also be a potential strategy to radiosensitize cancer cells; however, pharmacological inhibition of STAT for radiosensitization is not as far along in the drug development process, as compared to that of NF-κB inhibitors. Both transcription factors, NF-κB and STAT-3, regulate the expression of pro-inflammatory genes and cytokines that suppress apoptosis and induce invasion, metastasis, and angiogenesis processes, contributing to tumor cell radioresistance [reviewed in Di Maggio et al. 2015]. IR-induced IL-1β expression is one example of inflammatory IR response favoring tumor cell invasion and metastasis. Breast cancer patients have elevated IL-1β plasma levels persistent for a few weeks after radiotherapy (Sepah and Bower 2009) and in vitro studies demonstrate that IL-1β is involved in breast cancer cell invasion induced by IR (Paquette et al. 2013).

Irradiated tumor cells release several factors, including cytokines, involved in biological effects not only in irradiated cells but also in non-irradiated cells. There are three forms of non-target effects (NTEs) in radiotherapy, namely (1) bystander effect; (2) cohort effect; and, (3) abscopal effect (Wang et al. 2018). The bystander effect is defined as signals from irradiated tumor cells to neighboring non-irradiated cells. Cohort effects are responsible for the overall radiobiological response in irradiated cells that results from the direct energy deposition to target cells combined with indirect signals emitted from the neighboring irradiated cells. Abscopal effects are dependent on distant non-irradiated cells, which can also respond to irradiation consequences. These effects are mediated primarily by immune cells, such as T cells. In addition to nitric oxide and ROS, cytokines, such as tumor necrosis factor alpha (TNF-α), interleukin 8 (IL8), and transforming growth factor beta (TGF-β), have been implicated as a source of NTEs (Iyer et al. 2000; Gandhi and Chandna 2017).

4.2 Beyond Cytokines. The Role of Lipid Mediators Produced by Cancer Therapy

4.2.1 Prostaglandin E2 (PGE2)

In addition to cytokines, other mediators of inflammation are secreted after anticancer treatments and contribute to pro-tumorigenic signaling pathways that are critical for tumor growth, immunosuppressive microenvironment, and therapy resistance. In this chapter, we emphasize the involvement of lipids as mediators of inflammation upon anticancer treatment. Huang-Li demonstrated that apoptotic tumor cells stimulate the proliferation of a small number of living tumor cells, resulting in an accelerated tumor repopulation. In this study, they demonstrated that ionizing radiation induces apoptosis by activating caspase-3, which is the master "executioner" of apoptotic cell death and in parallel generates PGE2, a potent growth-stimulating signal of surviving tumor cells. In accordance with these findings, (Kurtova et al. 2015) it has been shown that PGE2 secreted by chemotherapy-induced dying cells promotes neighboring cancer stem cell repopulation, contributing to chemoresistance and indicating a role for PGE2 in tumor repopulation.

PGE2 belongs to the prostanoid family of lipids and is enzymatically synthesized from membrane phospholipids oxidation by cytoplasmic phospholipase A2 (PLA2), releasing arachidonic acid (AA). Free AA is converted to prostaglandin G2 (PGG2), which is subsequently reduced to PGH2 by the cyclooxygenase (COX) enzyme. Finally, PGH2 is metabolized to PGE2 through one of three PG terminal synthases: [microsomal PGE synthase-1 (mPGES-1 and mPGES-2)] and cytosolic PGE synthase (cPGES). Upon its biosynthesis, PGE2 binds to their cognate cell-surface receptors, designated EP1–EP4, either in an autocrine or paracrine fashion (Sugimoto and Narumiya 2007).

Among prostanoids, PGE2 is the predominant member found in many cancers, including colon, lung, breast, and head and neck cancer, and predicts poor prognosis (McLemore et al. 1988; Rigas et al. 1993; Wang and Dubois 2004; Hambek et al. 2007). Several studies have demonstrated a key role of PGE2 in promoting tumor progression by inducing cellular proliferation and angiogenesis, enhancing invasiveness, making cells resistant to apoptosis, and modulating immunosuppression [reviewed in Wang and Dubois 2010 and Finetti et al. 2020].

Secreted PGE2, contributes to the inhibition of antitumor immune responses by mediating immune cells [myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), dendritic cells (DCs), natural killer (NK) T cells, and regulatory T cells (Tregs)] to establish a tumor immunosuppression microenvironment [reviewed in Finetti et al. 2020]. PGE2 controls MDSC differentiation, recruitment, retention, and activation (Yang et al. 2015; Porta et al. 2020). It has been extensively described that PGE2 regulates macrophage polarization toward an M2 polarization (Yin et al. 2020) and also controls the recruitment of these immune cells into the tumor (Oshima et al. 2011). Tumor-derived PGE2 plays a key role in controlling DC differentiation, inhibiting the antigen presentation ability of

BM-derived DCs and favoring DCs role of T cell tolerance instead of antitumor immunity. Notably, PGE2 secreted by tumor cells suppresses NK cell activity (Wang and DuBois 2018). In addition, PGE2 inhibits T cells proliferation, regulates CD4+ T cells toward Th2 development, and inhibits antitumor cytotoxic T lymphocyte (CTL) responses (Sharma et al. 2005; Shimabukuro-Vornhagen et al. 2013; Basingab et al. 2016).

PGE2 immunosuppression can contribute to immunotherapy resistance. Interestingly, exposure of PBMCs to PGE2 previous to stimulation results in a decrease of proliferating T cells and in parallel induces the expression of the co-inhibitory receptors, PD-1 and TIM3. Additionally, inhibiting PGE2 partially restores T cells proliferation (Gorchs et al. 2019). Another evidence that PGE2 is related to immunotherapy resistance is that PGE2 signaling through EP2 and EP4 receptors present in cytotoxic T lymphocytes (CTL) contributes to its suppressive function. Moreover, simultaneous blockage of PD-1 and PGE2 EP2 and EP4 receptors restore CTLs cytotoxic functions (Miao et al. 2017). In a murine model, it was observed that tumor cells induce PD-L1 expression in myeloid cells which exhibits upregulation of PGE2-forming enzymes COX2 and microsomal PGE2 synthase 1 (mPGES1). The pharmacologic inhibition of these two enzymes reduces tumor-induced PD-L1 expression in myeloid cells (Prima et al. 2017). Indeed, preclinical models shows that COX inhibitors synergize with anti-PD-1 mAb (Zelenay et al. 2015). Combination of celecoxib, a selective COX2 inhibitor, and anti-PD-L1 inhibit PD-L1 expression in myeloid cells together with a reduction in murine melanoma and breast cancer progression (Li et al. 2016). In accordance with these findings, COX2/PGE2 axis inhibition can render tumor cells susceptible to immune control and might contribute to unleashing anticancer immunity, emerging as an adjuvant strategy to PD-1 blockade immune-based therapies.

All these reports demonstrate the PGE2 role in promoting pro-tumoral characteristics and favoring an immunosuppressive tumoral niche which leads to tumor growth. Thus, interference in PGE2 production could be an alternative to prevent tumor progression and reprogram tumor immunity. PGE2 production can be reduced by non-steroidal anti-inflammatory drugs (NSAIDs) which inhibit COX, the main enzyme involved in PGE2 production. Indeed, the contribution of the lipid mediator PGE2 to cancer development was evidenced by epidemiological observations showing that regular use of NSAID aspirin reduces mortality, metastasis, and incidence risk of various solid tumors (Veettil et al. 2017; Lin et al. 2018; Ma and Brusselaers 2018; Cho et al. 2020). However, the use of current targeting PGE2 therapies, NSAIDs, or COX-2 selective inhibitors (COXIBs) is limited due to their unacceptable cardiovascular and gastrointestinal side effects associated with their global proteinoid suppression. To avoid toxicity and achieve efficacy in reducing PGE2 levels, it is more clinically plausible blocking PGE2 biosynthesis by selectively targeting PGE2 EP receptors. Indeed, all PGE2 pro-tumorigenic roles are dependent on the activation of PGE2 EP receptors and they can be expressed on the surface of both tumor and tumor stromal cells. In this context, various small-molecule ligands targeting EP receptors have been identified, one example is the antagonist ONO-8711 specifically blocks EP1 receptors and exhibits chemopreventive activity

in several animal models of epithelial malignancy (Kawamori et al. 2001). However, EP antagonists have not been available in clinics up to now. Therefore, it is crucial to develop more effective and selective strategies to diminish PGE2 levels in cancer patients as an adjuvant strategy to conventional and immune-based cancer therapies.

4.2.2 Platelet Activating Factor (PAF)

Conventional chemotherapy and radiotherapy generate another lipid mediator of inflammation, platelet activating factor (PAF). Considering that PAF is synthesized in response to stress, including agents that induce DNA damage (Barber et al. 1998) and free radical formation (Lewis et al. 1988), it is intuitive to think that chemotherapy and radiotherapy may generate PAF. Indeed, a large number of studies have demonstrated that different anticancer therapy agents can induce overproduction of PAF agonists and increase the expression of its receptor, PAF-R, in diverse tumor cells. Chemotherapeutic agents (etoposide, dacarbazine, and cisplatin) and radiotherapy can generate native PAF and PAF agonists in melanoma tumors. Furthermore, PAF/PAF agonists generation by chemotherapy was partially blocked by antioxidants and PAF-R activation inhibits chemotherapy effectiveness by subversion of tumor-host immunity through regulation of Tregs in a COX-2-dependent process (Sahu et al. 2014, 2016). Additionally, chemotherapy induces PAF-R expression and PAF-R antagonist chemosensitizes melanoma cells in vitro and in vivo (Onuchic et al. 2012).

PAF is a potent pro-inflammatory lipid mediator which under physiological conditions is produced in small and continuous amounts by de novo synthesis and participates in membrane biogenesis. However, upon acute inflammation, such as that induced by radio and chemotherapy, large amounts of PAF are produced. Binding of PAF/PAF agonists molecules to its receptor activates many downstream survival pathways, including mitogen-activated protein kinase (MAPK) cascade and nuclear factor kappa-beta (NF-kB) (Ishii and Shimizu 2000). The role of PAF in tumorigenesis is complex, it can contribute to homeostasis by limiting cell proliferation and inducing apoptosis, and it can also promote tumorigenesis by stimulating cell growth, inhibiting DNA repair, inducing angiogenesis and metastasis (Tsoupras et al. 2009; Lordan et al. 2019). The balance between these opposing forces determines the final effect of PAF on tumorigenesis.

The role of PAF in inducing immunosuppression was well described in studies designed to define the molecular events involved in UV-induced immunosuppression. It has been shown that UVB-irradiated keratinocytes generate PAF/PAF agonists and administration of PAF-R antagonists in UV-irradiated mice inhibits UV-induced immune suppression. The general idea is that UVB irradiation generates PAF agonists which signal through PAF-R and activate downstream survival and immunosuppressive pathways, including the production of cytokines [e.g., TNF-α, IL-6, IL-10, COX-2, and PGE2 (revised in Ullrich 2005)]. It has been shown that this systemic immunosuppression contributes to the establishment of

murine melanoma tumors. Administration of cPAF enhances B16F10 tumor growth in vivo; however, this effect is not observed in immunodeficient NOD SCID mice, suggesting that it depends on targeting PAF-R on host immune cells (Sahu et al. 2012). This notion was also supported by animal models, whereby growth of two murine tumors, B16F10 melanoma and TC-1 carcinoma, was reduced in PAF-R KO, as compared to wild-type animals. Considering that TC-1 cells express PAF-R, whereas B16F10 do not this data reinforce the role of PAF-R signaling in immune cells. It also observed an increase in M2 macrophages frequency and intratumoral neutrophils, $CD4^+/CD8^+$ lymphocyte infiltration in PAF-R KO animals. These data suggest that tumor-derived PAF-R ligands regulate the recruitment and phenotype of immune cells, favoring tumor growth (da Silva et al. 2017). Accordingly, exogenous PAF was shown to potentiate the production of anti-inflammatory IL-10 by LPS-stimulated macrophages, driving them toward a regulatory phenotype (Ishizuka et al. 2016).

Similar PAF regulatory effects were also observed in LPS-stimulated murine DC. PAF-R is present on the DC membranes and its activation mediates DC phenotype and function. Koga et al. (2013) demonstrated that PAF-R activation during DC maturation resulted in a downregulation in antigen-presenting capacity of DC through the increased production of IL-10 and PGE-2 mediated by PAF-R. Moreover, in vitro treatment of DCs with PAF-R antagonists induce higher CD4+ T cell proliferation, indicating that the adaptive immune system is also involved in PAF-R-dependent tumor growth. This notion is supported by the evidence that exogenous cPAF does not affect tumor growth in immunodeficient NOD SCID mice, indicating the participation of Tregs in this pro-tumoral PAF-R response. Tumor growth mediated by PAF-R activation can be inhibited by depleting antibodies against Tregs and IL-10. Essentially, UVB-generated PAF agonists target host immune cells to orchestrate a systemic immunosuppression that favors murine melanoma tumor growth (Sahu et al. 2012). In accordance with these findings, it is appropriate to conclude that activation of PAF/PAF-R axis plays an important role in the regulation of inflammatory and immune responses.

Several chemotherapy regimens and mainly radiotherapy induce reactive oxygen species (ROS) production which can oxidize membrane phosphatidylcholine leading to PAF agonist production. Secreted PAF binds to PAF-R and in positive feedback, PAF-R activation promotes the synthesis of bona fide PAF. This amplified production of PAF results in an enhancement of PAF/PAF-R downstream biological processes discussed above. Briefly, PAF can signal in an autocrine way to tumor cells, stimulating proliferation and migration. Additionally, a paracrine signal of PAF to endothelial cells favors angiogenesis and to immune cells, mainly macrophages and T cells, promote immunosuppression by shifting these cells toward an immunoregulatory phenotype (Chammas et al. 2017).

Independently of ROS generation, all anticancer therapies result in cell death. As discussed above, when cells die they are engulfed by specialized phagocytes, the macrophages, through the exposure of several molecules on their surface which are recognized by macrophage receptors [reviewed in Gregory and Devitt 2004]. Importantly, macrophages do not simply engulf and digest apoptotic cells, they respond to

these cells by changing the profile of pro- and anti-inflammatory mediators that they release. Accordingly, it has been shown that the professional scavenger role of macrophages is dependent on PAF-R activation which reprograms these cells toward a regulatory phenotype. The phenomenon of efferocytosis of apoptotic and necrotic cells can be decreased by pretreating macrophages with PAF-R antagonists (de Oliveira et al. 2006). Another piece of evidence shows that efferocytosis of apoptotic cells requires the engagement of both CD36 and PAF-R (Rios et al. 2013). Coculture of mice bone marrow-derived macrophages with apoptotic thymocytes in the presence of PAF-R antagonists or specific antibodies against CD36 inhibited the phagocytosis of apoptotic cells by approximately 70–80%. Blocking PAF-R or CD36 also prevented efferocytosis-induced production of IL-10, inhibiting the regulatory cytokine profile IL-10 (high)/IL-12p40 (low) (Ferracini et al. 2013). All these reports indicate that the macrophage role of apoptotic cell clearance depends on PAF/PAF-R activation and is associated with a modulation of macrophage suppressor phenotype that contributes to tumor growth.

Additionally, apoptotic cell clearance results in immune implications dependent on the PAF/PAF-R axis that contribute to tumor repopulation. In animal models, coinjection of apoptotic cells promotes tumor growth from a sub tumorigenic dose of melanoma cells or Ehrlich ascites tumor. Moreover, results demonstrated that PAF-R antagonists significantly inhibited the tumor growth-promoting effect of apoptotic cells concomitant to the inhibition of early neutrophil and macrophage infiltration (de Oliveira et al. 2010; Bachi et al. 2012). Irradiated TC-1 cancer cells induce the proliferation of live TC-1 cells in vitro and in vivo in a PAF-R-dependent way. Tumor cell repopulation was correlated with increased infiltration of tumor-promoting macrophages (CD206+) (da Silva et al. 2017). It is worth noting that besides the development of PAF-R antagonists, none are in clinics due to toxicity issues and as far as we know there are no therapeutic strategies available to interfere in PAF synthesis. In this context, it would be of interest to study a putative beneficial effect of the combination of new strategies to inhibit PAF/PAF-R axis and radio or chemotherapy.

4.2.3 Resolvins

The notion that therapy-generated tumor cell death is a double-edged sword is now well accepted. Several manuscripts support this concept and show that tumor cell debris generated throughout chemotherapy, radiotherapy, or target therapy (Huang et al. 2011; da Silva et al. 2017; Sulciner et al. 2018) stimulate tumor growth. As previously discussed, PAF/PAF-R is involved in the dual effect of cytotoxic cancer treatments. Additionally, another lipid is recently reported to have a key role in tumor repopulation phenomenon. Proresolving lipid autacoids, specific RvD1, RvD2, or RvE1, stimulate the resolution of tumor-promoting inflammation (Sulciner et al. 2018). Interestingly, in this latter study, a critical role for phosphatidylserine in cell debris-stimulated tumors was described through the use of neutralizing anti-PS

antibodies. Anticancer therapies induce sterile inflammation by apoptotic cells release of inflammation "danger signals" that can either activate or suppress antitumor immunity. Stimulation of debris clearance process, in order to promote the termination of the inflammatory process, represents a new approach to inhibit tumor progression, growth, and recurrence (Serhan and Levy 2018). Thus, resolvins (i.e., RvE1, RvD1, and RvD2) can polarize the pro-tumorigenic and pro-inflammatory macrophages present in therapy-induced inflammatory microenvironment toward a pro-phagocytic state, inhibiting further pro-inflammatory cytokine secretion. Likewise, other lipid mediators derived from the activity of epoxide-hydrolases phenocopy the activities of resolvins (Zhang et al. 2014; Gartung et al. 2019; Fishbein et al. 2020). Findings provided by these reports further the interest in determining specific conditions in which therapy-generated cell debris activates or suppresses antitumor immunity to allow the design of new therapeutic approaches more efficiently in preventing tumor growth and recurrence.

4.3 Modulating Inflammation for Cancer Therapy by Nanobiotechnology

In cancer therapy, inflammation is an undesired but prevalent side effect that complicates treatment and, in some cases, can be a danger to the patient's health. Because of the possibility for severe adverse reactions, many developing treatments are delayed or stopped as they are deemed unsuitable for clinical use (Pecot et al. 2011). Furthermore, the induction of pro-inflammatory cytokines responsible for such inflammatory reactions also plays various roles throughout the hallmarks of cancer by promoting tumor growth and invasion (Dinarello 2006). Upstream of cytokine production in the cellular environment are pattern recognition receptors (PRRs) which activate a cascade of signals upon interactions with pathogen-associated molecular patterns (PAMPs) or in response to damage-associated molecular patterns (DAMPs) (Takeuchi and Akira 2010). These innate pathways are well-adapted to protect against pathogens, yet also can trigger the production of pro-inflammatory cytokines in response to cell death, even when favorable in the case of cancer therapies (Hernandez et al. 2016).

As a strategy for targeted and personalized medicine, nanotechnology offers a modular approach to overcoming unfavorable immune responses while maintaining the therapeutic effects of formulations. Established candidates for drug delivery can be selected based on their immunological profiles, even incorporating some known biological structures and PAMPs to fit the application as needed. For cancer therapies, the ideal candidates are those which can generate antitumor responses via inflammation without overstimulating a more chronic inflammatory response and ultimately aggravating cancer (Ilinskaya and Dobrovolskaia 2014; Barber 2015). Approaches may also focus on promoting anti-inflammatory activities or overall immunosuppression, which has its own consequences in the form of potential

myelosuppression, thymic suppression, and overall lowered immune function (Ilinskaya and Dobrovolskaia 2014). Nanobiotechnology can be used to deliver anti-inflammatory drugs to increase their overall solubility and bioavailability (Ilinskaya and Dobrovolskaia 2014). For example, dendrimers have been used as carriers for methotrexate and indomethacin in order to reduce inflammation, while the dendrimers themselves are anti-inflammatory, owing to their generation and surface group functionalization (Chandrasekar et al. 2007; Chauhan et al. 2009). Specific targeting of diseased cells only can be achieved using nanoplatforms in order to recruit particular cell populations to zones of inflammation. An example of this is the use of folic acid on chitosan nanoparticles to deliver siRNAs against COX-2 into activated macrophages (Yang et al. 2014). The highly customizable approach of nanotechnology allows for combinatorial strategies, such as for the codelivery of anti-inflammatory agents and targeting moieties.

Some of the foremost targets of PRRs are nucleic acids, owing to their roles in pathogenic invasion, but specifically for PAMPs which indicate the presence of non-self-genetic materials over self. As a result, nucleic acids offer a means to modulate therapy-induced inflammation and can be tailored, based on their sequences and resulting structures, to vary the resulting productions of pro-inflammatory to anti-inflammatory cytokines as desired. Agonists of the cGAS-cGAMP-STING pathway, for example, have been utilized for the development of vaccine adjuvants as well as cancer immunotherapies to activate antitumor T cell responses (Barber 2015). In addition to their immune recognition, nucleic acids retain their functional abilities to encode proteins, control posttranscriptional gene regulation, and interact with other classes of biomolecules, which then allows them to serve as vaccines encoding neoantigens, mRNAs for immunomodulation, viral mimics, and inducers of gene silencing in cancer therapy (Bisogno and Keene 2018; Lin et al. 2020). Nucleic acids have been demonstrated to silence the genes for immune checkpoints, play roles in cytokine regulation, and also act as vaccines (Lin et al. 2020). For example, siRNAs against TNF-α can be delivered to cells to reduce inflammation (Howard et al. 2009).

Individual strands of short synthetic nucleic acids can also be rationally designed to self-assemble into well-defined nucleic acid nanoparticles (NANPs), which are at the center of an emerging technology with the potential to manipulate and control biological processes at the molecular level (Dobrovolskaia 2019; Panigaj et al. 2019). NANPs may be composed of either DNA or RNA or their chemical analogs, all of which are programmed to interact via canonical Watson–Crick or non-canonical base pairing to result in the reproducible formation of specific nanostructures. NANP platforms have been developed to serve as biocompatible nanoscaffolds for the simultaneous codelivery of functional biomolecules (Afonin et al. 2014; Halman et al. 2017), therapeutic nucleic acids (Afonin et al. 2011), or fluorescent arrays (Yourston et al. 2020). However, in the biological environment outside of cells, NANPs are effectively invisible to the immune system. Due to their macromolecular structure, NANPs alone are too anionic to be efficiently taken up by cellular membranes or immune cells (Hong et al. 2018). The only way for a given NANP to enter a cell is thus via transfection using a delivery carrier, which is the only route to accessing the intracellular PRRs responsible for immunostimulation.

As was recently discovered, NANPs' interactions with the immune system can be controlled based on the structure, dimensionality, and composition of the NANP (Guo et al. 2017; Halman et al. 2017; Johnson et al. 2017, 2020; Rackley et al. 2018; Chandler and Afonin 2019; Hong et al. 2019; Ke et al. 2019; Dobrovolskaia and Afonin 2020), as well as the type of carrier used for NANPs' delivery (Dobrovolskaia and McNeil 2015; Halman et al. 2020; Avila et al. 2021).

Toll-like receptors (TLRs) are a particular class of PRRs which are produced and utilized by the immune system to interact with nucleic acids as a defense against foreign sequences. In humans, TLRs 3, 7, 8, and 9 are endosomal PRRs specific to nucleic acids and therefore are also involved in the recognition of NANPs composed of them. While these PRRs bind based on a variety of parameters, there are general structural trends to their activation. For instance, TLR3 binds to double-stranded RNA. This pathway leads to activating type I interferon production (Alexopoulou et al. 2001; Ranjith-Kumar et al. 2007; Leonard et al. 2008). TLR7 and TLR8 interact with single-stranded RNA (Heil 2004; Lund et al. 2004) and preferentially bind to uridine-rich sequences (Zhang et al. 2018). The MyD88 pathway is activated and results in the expression of type I interferons and pro-inflammatory cytokines (Heil 2004; De Marcken et al. 2019). TLR9 recognizes unmethylated CpG-rich DNA motifs and also induces the expression of type I interferons and pro-inflammatory cytokines (Latz et al. 2004). Besides endosomal PRRs, there are also several cytosolic sensors for non-self-nucleic acids. For example, the cGAS-cGAMP-STING pathway detects double-stranded DNA (Nakhaei et al. 2010; Motwani et al. 2019). RIG-I recognizes triphosphorylated RNAs (Hornung et al. 2006; Loo and Gale 2011) while longer double-stranded RNAs can be identified by MDA5 (Chandler et al. 2020). As a result of these trends in detection, the dimensionality, composition (DNA vs RNA), and functionalization with therapeutic nucleic acids on the NANP scaffold can determine the specific PRR and guide the resulting immune response (Chandler et al. 2020). Importantly, varying the sequence of a specific NANP does not seem to affect the immunostimulation so long as its structure is maintained (Chandler et al. 2019). The type of carrier also influences the route of delivery and thus the interactions which determine the response of the immune system (Halman et al. 2020; Avila et al. 2021).

The tailorability of nanotechnology is well-exemplified by NANPs, as variation in designs can be utilized to selectively aid in turning off or avoiding pro-inflammatory reactions or activating them as needed. For example, when delivered with a lipid-based carrier, three-dimensional RNA cubic NANPs have been consistently shown to interact with TLR7 for the downstream production of type I interferons, while three-dimensional DNA cubic NANPs are largely immune quiescent in human immune cells (Hong et al. 2018). Further investigations into the structure–activity relationship of NANPs to link a library of thoroughly physicochemically characterized NANPs with their associated panel of responses and their relative magnitudes hold much promise as an asset to effectively modulating the immune response. With the right combinations selected per patient, this technology could allow for more careful modulation of the inflammation associated with cancer therapy.

Much of the groundwork has been laid out by those that realized nucleic acids are much more functional beyond solely carrying information. As nucleic acid nanotechnology is further studied and fine-tuned, better treatments in favor of patient health grow closer to reality. Currently, there are several RNA-based therapies recently approved by the US Food and Drug Administration to treat a number of conditions, with many more in the pipeline (Afonin et al. 2020). While the systematic recognition by the innate immune system has previously challenged therapeutic nucleic acid development, the new outlook of harnessing these established routes for favorable modulation could allow for advanced applications in cancer therapy. This gap in knowledge requires further investigations of such therapies to produce safe and effective treatments (Afonin et al. 2020).

4.4 Conclusion and Prospects

Therapy induces the secretion of inflammatory mediators by dead or dying cells that recruit the immune system. In the first moment, these mediators orchestrate the clearance of dead cells and elicit an antitumoral immune response. However, in the long run, the pro-inflammatory mediators generated by dead cells induce the survival of the remnant tumor cells and promote a microenvironment that favors tumor recurrence. The challenge posed to the future is to identify clearly distinct phases in the post-therapy continuum in which inflammation could be either boosted or blocked. Understanding the different phases of therapy-induced inflammatory responses will allow further development of anticancer therapies that will likely exploit nanocarriers or nano-approaches that shape the immune/inflammatory landscape within tumors.

Acknowledgements Research reported in this publication was supported by the National Institute of General Medical Sciences of the National Institutes of Health under Award Numbers R01GM120487 and R35GM139587 (to K.A.A), Fundação de Amparo à Pesquisa do Estado de São Paulo (2017/50029-6, to RC and KAA) and Conselho Nacional de Pesquisa e Desenvolvimento (426714/2016-0 and 305700/2017-0, to RC). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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