Inflammatory response, reactive oxygen species, programmed (necrotic-like and apoptotic) cell death and cancer

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Abstract

In this short review we attempt to establish and/or strengthen connections between clinical, inflammatory manifestation of cancer, inflammatory processes driven by lipoxy-metabolites and their contribution to immortalized phenotype and apoptosis inhibition. Particularly the resemblance between symptoms of inflammation and signs associated with cancer chemotherapy and/or cytokine therapy is illustrated. In this context the role of apoptosis and necrosis in inflammation as well as the role of RedOx processes and lipid-oxidizing enzymes particularly cyclooxygenase-2 (COX-2) and also to lesser extend the 5-lipooxygenase (5-LOX) is highlighted. The multitude of biological effects of reactive oxygen species is shortly summarized and some aspects of it are being discussed in greater detail. Apoptotic cell death is discussed in the context of the "resolve-phase" of an inflammatory response. The disturbance of apoptosis is mainly deliberated in the framework of insufficient removal of immuno-effector cells that may cause autoimmunity. The role of COX-2 in apoptosis resistance is being highlighted mainly in the context of malignant transformation. The mechanism of cell death (apoptotic or necrotic) and its influence on the immune system and potential benefits of necrotic cell death induction during cancer chemotherapy is indicated.

Key words: apoptosis, caspases, cancer, COX-2, inflammation.

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Abbreviations: AA, arachidonic acid; COX, cyclooxygenase; DR5, death receptor 5; GSH, L-γ-glutamyl-L-cysteinyl glycine; 12-HETE, 12-hydroxyeicosatetraenoic acid; HPETE, hydroxyeicosatetraenoic acid; iNOS, inducible nitric oxide synthase; 5-LOX, 5-lipooxygenase; LPS, lipopolysaccharide; LXA4, lipoxin-A4; NSAIDs, nonsteroidal anti-inflammatory drugs; ROI, reactive oxygen intermediates; PGE2, prostaglandin-E2; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-α; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; UV, ultraviolet radiation; zVAD-fmk, benzyloxycarbonyl-Val-Ala-Asp-fluoromethyl ketone.

Introduction

Reactive oxygen species (ROS) are associated with the inflammatory response and frequently they contribute to the tissue damaging effects of inflammatory reactions [1-3]. On the other hand they are important mediators of programmed cell death induced by TNF [4,5]. Moreover, in some experimental models, when applied at low concentration they are capable in stimulating cell growth [6,7]. Furthermore, at intermediate concentrations ROS induce apoptosis whereas at higher concentrations it induce necrotic cell death [8,9]. The mutagenic effect of ROS is well established. It contributes to DNA damage evoked by ionizing radiation and certain chemical cycling oxidants (eg. doxorubicin [10] or paraquat, [11]), and under certain circumstances it may lead to cancer.

Inflammation, which was recognized as a simple allergic reaction for decades, is currently being considered to underline pathophysiology of a much broader spectrum of diseases than previously expected. The complex interplay of cellular and humoral mediators during inflammation is unfolding but our understanding of the inflammatory reaction is still incomplete [12,13]. Viruses, frequent pathogenic inducers of inflammatory response, have acquired a number of elaborated ways to evade both, the apoptotic response and inflammatory processes [14,15].

The inflammatory process initiated in response to a pathogen or an injury is maintained at a certain, adequate level till the offending stimulus is neutralized, after which the reaction resolves on its own. In an auto-immune disorder, a harmless antigen is mistaken by the immune system as begin foreign, thus initiating the inflammatory reaction. The persistence of a stimulus, that physiologically resides in the organism, prevents the natural, resolving mechanisms from prevailing [16]. As a result one's own defense mechanism can turn into a perpetuator of a persistent injury which although not fatal, can lead to loss of function of the organs involved.

Additionally, many of the mediators can leak from the local region and initiate inflammatory reactions elsewhere [17]. Animal experiments have been extremely useful in understanding the entire inflammatory reaction since they demonstrate a complete window of events, from the time when the stimulus is given till the reaction naturally resolves [18,19].

ROS and inflammation

ROS formation and degradation are key components of the metabolism of aerobic organisms. Certain levels of ROS are required for normal cell functions, but if in surplus, they will cause oxidative stress [6,20,21]. ROS like superoxide, hydrogen peroxide and lipid hydroperoxides can regulate the activities of several kinases, transcription factors, cell death machinery and proteins such as COX-2 and iNOS [21-24]. ROS also function as second messengers in intracellular signal transduction pathways [6,20,25]. However, upon prolonged activation in vivo, the deleterious effects of ROS and enzymes take an upper hand in the destruction of the tissues by affecting the structure-function model of all macromolecules, sometimes irreversibly. ROS play a major role in the joint destruction by their ability to transform proteins to autoantigens and/or increase the susceptibility of proteins to degradation. Neutrophils play a crucial role in the development and manifestation of inflammation and they are the major source of free radicals at the site of inflammation. Lipid peroxidation mediated by free radicals might yield a large number of reactive aldehydes and also lipid peroxides which are causally involved in pathophysiological changes associated with oxidative stress in cells and tissues [26,27]. GSH (L-γ- glutamyl-L-cysteinyl glycine) is an ubiquitous thiol-containing tripeptide, which plays a key role in cell biology. It is implicated in the cellular defense against xenobiotics and naturally occurring deleterious compounds, such as free radicals and hydroperoxides. GSH status is a highly sensitive indicator of cell functionality and viability [28,29]. RedOx status with increased GSSG formation is a key factor that mediates apoptosis in neutrophils and macrophages [30,31]. The increased level of GSSG concentration point to the prevailing oxidative stress and indicates ongoing ROI detoxification. The overwhelming level of intracellular ROI and GSSG indicates a disturbance in the RedOx status of the cell, a condition that may be followed by apoptosis. Many of the agents capable of inducing ROS, such as intermediate concentration of H202, UV light and ionizing radiation [9,21,32] are also known to evoke apoptosis.

Cyclooxygenases are key enzymes in the prostaglandin synthesis. The inducible isoenzyme COX-2 plays a pivotal role as a mediator of inflammation. COX-2 enzyme activity itself is sensitive to, and regulated by the RedOx status of the environment [33]. Antioxidants inhibit the expression of COX-2 in human alveolar macrophages [34]. One regulatory element that can control the COX-2 expression is NF-κB activity. NF-κB and AP-1 transcription factors are activated by changes in the RedOx status of the cell [23]. The AP-1 subunits, c-fos and c-jun, are regulated by oxidant response elements and are induced by lipopolysaccharide (LPS).

Oxidized phospholipids were shown to inhibit COX-2 expression induced by LPS in macrophages by interfering with the NF-κB/lκB, MAP kinase and ERK2 pathways in atherosclerotic lesions [35]. Based on the above data, it can be hypothesized that conditions of oxidative stress/antioxidant imbalance impair the capacity of macrophages to correctly contribute to the resolution of the inflammatory processes. The inhibition of the COX pathway increases formation of ROS through peroxidative cleavage of 5-hydroxyeicosatetraenoic acid (5-HPETE), and hence 5-LOX inhibitors would attenuate this effect. The present study demonstrated the effectiveness of anti-oxidants in reducing the inflammatory reaction, expression of COX-2, iNOS levels and oxidative stress by inducing apoptosis in the inflammatory cells. These studies thus indicate, the importance of ROS in bringing about the inflammatory reaction and also the therapeutic potential of anti-oxidant mixture in reducing inflammation. Several attempts have been made to turn naturally occurring antioxidants into anti-inflammatory agents [36-40], but their successful clinical implementation was infrequent. The relative lack of effectiveness of this approach may be related to the fact that inhibition of the expression of genes involved in inflammatory response alone may be insufficient to fully block the process. Apoptotic mechanisms that remove superfluous immunocompetent cells need to be in place as well (see below).

p53 and inflammation

Transcriptional activation of p53 in the area of inflammation is probably induced in response to the toxic environment of the inflamed tissue. The local production of oxygen radicals, nitric oxide, cytokines, eicozanoids etc. may lead to the accumulation of normal p53 [41]. The overexpression of wild type p53 in inflammatory disorders such as ulcerative colitis and rheumatoid arthritis [42], cancers [43], autoimmune encephalomyelitis [44] and various animal models of chronic inflammation [45] have been well documented. The central involvement of p53 in initiating apoptosis after exposure to a variety of cellular stress inducers is presently becoming established [46,47]. The increased p53 levels and augmented apoptotic cell death is observed mainly in the resolution of inflammation [48]. The inhibition of p53-dependent apoptotic mechanisms in inflammatory effector cells may contribute to the transition of the acute inflammatory response into the chronic phase of inflammation. Mediators of inflammatory response may influence the expression level of p53. For example, p53 expression was reduced in the presence of COX-2 inhibitor celecoxib, thus p53 may be

directly regulated by inflammatory mediators. On the other hand, COX-2 itself has been reported to regulate the expression of p53 and in turn it is regulated by NF-κB, a transcription factor that is well known for modulation of expression of inflammatory molecules [49,50] in vitro.

The role of apoptosis in inflammation

In order to cease the inflammatory response the infiltration of inflammatory effector cells has to be stopped and the existing population of pro-inflammatory cells must be eliminated without provoking the release of pro-inflammatory mediators [51]. This is achieved by the apoptotic process that normally involve activation of the proteolytic cascade of caspase family proteases [52-54]. An important determinant of the resolution of inflammation is apoptotic removal of leukocytes with subsequent clearance of the apoptotic bodies by phagocytosis [55,56]. Recent publications also show active suppression of pro-inflammatory cytokine production during phagocytosis of apoptotic cells (reviewed in [56]). Therefore, the development of therapeutic strategies aimed at inducing apoptosis in rheumatoid arthritis and other chronic inflammatory disorders is an attractive goal since (I) reduced apoptosis may play an important role in the pathogenesis of chronic inflammation [57], and (II) promotion of apoptosis in the chronically inflamed tissue may have an anti-inflammatory effect by itself. This goal can be addressed in two ways: (1) by inducing apoptosis in the inflammatory effector cells, or (2) by inhibiting the anti-apoptotic mechanisms of these cells [58,59]. Reduced apoptosis of synovial cells has been described in residential synoviocytes as well as in inflammatory cells that are associated with the pathogenesis of rheumatoid arthritis [60,61]. Although a detailed understanding of mechanisms that prevent synovial fibroblasts from programmed cell death is lacking, several anti-apoptotic molecules have been identified. Among them, transcriptional regulators such as p53, NF-κB and Stat3, have been suggested to regulate apoptosis most prominently [49,62]. The increased apoptosis of immune effector cells in the resolution-phase of inflammatory response is associated with the increased expression of Apaf-1, the key component of apoptosome. Unlike during tissue remodeling for example, when the surrounding cells remove the bulk of dying neighbor cells, macrophages are the main cells that phagocytose apoptotic immune-effector cells during downscaling of the specific immune response. Phagocytosis triggers macrophage release of CD178 (Fas ligand), an event that may lead to the induction of the apoptosis of bystander leukocytes [63]. This will happen only towards the end of a successful inflammatory response since freshly stimulated T-cells are resistant towards CD95(Fas, Apo-1)-triggered apoptotic death [64,65]. Prolonged exposure of cultured human monocyte-derived macrophages to a cytokine cocktail including, GM-CSV, TNF, IFN-γ, IL-1β, IL-10, enhances their capacity to phagocytose apoptotic cells in vitro [66] suggesting that this process is dynamically regulated at the site of inflammation. LPS, a potent cofactor of macrophage activation in vitro, prevented apoptosis in human peripheral blood monocytes, allowing their maturation into macrophages [67]. Although the mechanism by which LPS promotes viability of monocytes is not clear, macrophage phagocytosis of apoptotic cells is accelerated by the endogenous lipooxy-metabolites like lipoxin-A4 (LXA4), [68] 12-hydroxyeicosatetraenoic acid (12-HETE) and prostaglandin-E2 (PGE2) [69].

COX-2 activity is an important component of all inflammatory reactions. Although there are no reports of COX-2-specific effects on apoptosis during inflammation, both isoforms of COX are known to have a significant role in apoptosis and cell survival as it has been observed in studies on cancer [70,71]. Furthermore, a higher number of apoptotic neutrophils was observed in COX-2 deficient mice rather than in COX-1 deficient mice [72] suggesting an anti-apoptotic role for COX-2. Overexpression of COX-2 has been linked to down regulation of apoptosis and thus to facilitation of malignant transformation in many cell types [73]. Thus, while the COX-2 – apoptosis link seems to be a normal physiological process, there are multiple lines of evidence indicating that inappropriate up-regulation of COX-2 prolongs the survival of malignant cells and leads to phenotypic changes associated with metastatic potential [61]. Overexpression of COX-2 inhibits death receptor 5 (DR5) expression and confers resistance to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced apoptosis in human colon cancer cells [74].

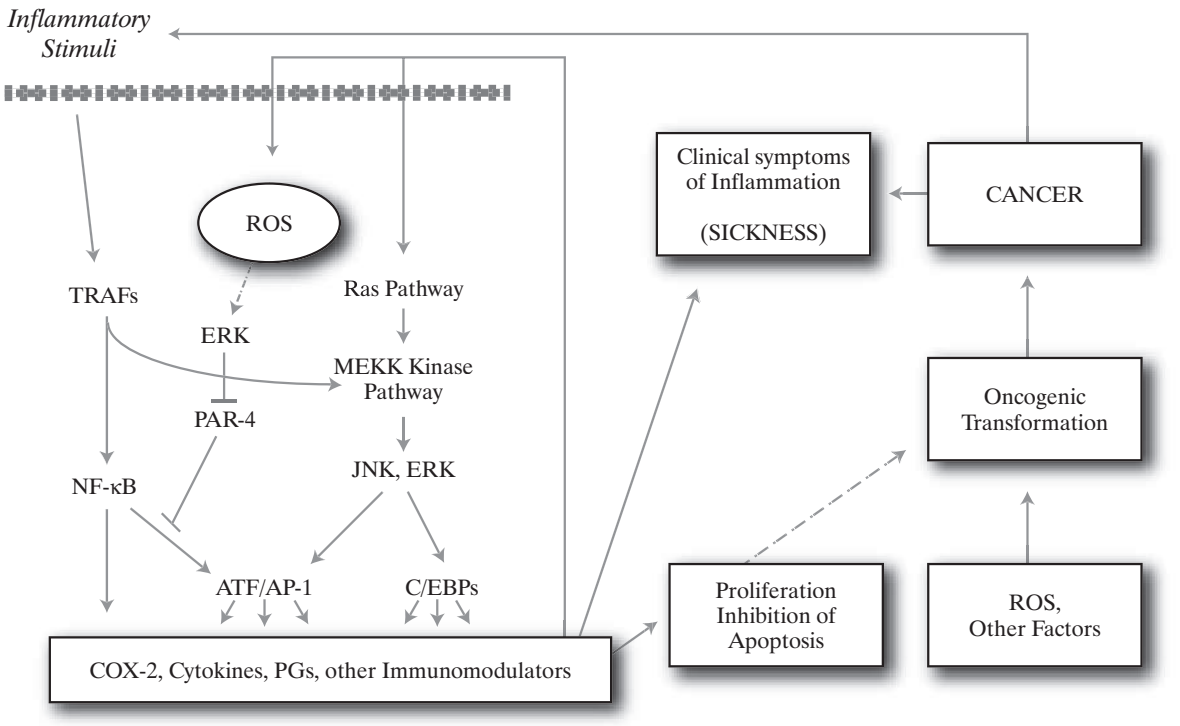
Accumulation of arachidonic acid (AA) activates sphingomyelinase activity, leading to production of apoptotic-inducer, ceramide. This accumulation has been shown both: 2 and you have 3 in primary fibroblasts, immortalized keratinocytes and epidermal cancers [75]. Celecoxib, a COX-2 inhibitor, induced apoptosis in various models of inflammation studied as well as in some experimental tumor models [76,77]. This pro-apoptotic action of celecoxib was shown to be COX-2 dependent [78] as well as independent [79,80]. However this observation also explains the reason why celecoxib is such a good anti-inflammatory agent, as it not only reduces the levels of PGE2, but also kills the inflammatory cells.

Cancer and inflammation

Inflammatory symptoms accompany malignant proliferatory diseases

Cancer patients frequently suffer from symptoms resembling an inflammatory response, resulting from the primary disease and/or from the treatment (*Fig. 1*). The symptoms include pain, gastrointestinal problems (e.g. nausea, diarrhea), wasting/ /cachexia, fatigue, cognitive impairments, anxiety, and depression. Symptoms can cause treatment delays or lead to premature treatment termination. It also may impair function, and rehabilitation, and cause significant distress to the patient [81,82]. Mechanisms related to stress/immune response may underlie or contribute to at least some of those symptoms [82,83]. This has been demonstrated in animal models of sickness behavior, which share symptoms with those patients with cancer. Sickness behavior refers to a constellation of physiologic and behavioral responses observed in animals after the administration of inflammatory agents or specific pro-inflammatory cytokines [84-88]. Sickness behavior can be elicited in animal models by bacterial infections and by administration of pathologic components

Figure 1. **Interplay between inflammatory stimuli, signaling pathways, and ROS, – effects on oncogenesis and clinical symptoms (sickness). The schema outlines signaling pathways involved in inflammation and it provides relation between inflammatory response, proliferation, inhibition of apoptosis and oncogenic transformation. The depicted signaling pathways synthesize the information provided in the main text. Some kinase signaling pathways have been adapted from the literature [155]**



of bacteria such as LPS. Physiologic components of sickness behavior are similar to these observed by cancer patients and they include acute-phase responses (fever, systemic depletion of body electrolites), pain (hyperalgesia), wasting, increased activity of the hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous system [85]. Behavioral components include a general decrease in activity, somnolence, cognitive impairment (impaired learning), decreased social interaction and exploration, decreased sexual activity, and decreased eating [89]. The responses characteristic of sickness behavior can also be elicited by systemic administration of pro-inflammatory cytokines including IL-1β, TNF, IFN-γ, and IL-2, administered subcutaneously, intravenously, or intraperitoneally [84-88,90--96]. Pro-inflammatory cytokines play a central role in preclinical models that focus more specifically on the symptom of peripheral neuropathic pain/hyperalgesia (hypersensitivity to cutaneous stimuli). Experimental animals, like humans, develop peripheral neuropathic pain following treatment with the chemotherapeutic agents commonly used to treat cancer, like vinca alkaloids, taxanes, and cisplatin [97-99]. In both humans [100] and animals, [101] exposure to γ-irradiation also often produces neuropathic pain-like syndromes and insensitivity to the analgesic properties of morphine. Peripheral neuropathy could be due, at least in part, to the induction of proinflammatory cytokines around nerve endings. For example, production by immune cells and/or cancer cells of the proinflammatory cytokines IL-1 β, IFN-γ, and TNF can be increased by exposure to paclitaxel, [102,103] cisplatin, [104] or irradiation [105].

Clinical evidence consistent with the role of inflammatory cytokines in symptom occurrence by cancer patients

The hypothesis that cytokines may play a mechanistic role in cancer-related symptoms is consistent with various clinical observations. Non-cancer patients who received cytokine therapy displayed many of the symptoms that are observed in cancer patients. For example, patients with hepatitis C virus infection and those with the acquired immunodeficiency syndrome (AIDS) who received IFN-α therapy endured symptoms of pain, fatigue, cognitive impairment, psychosis, and depression [106,107]. A similar symptom profile was observed among patients with renal cell carcinoma, chronic myelogenous leukemia, melanoma, all of whom received IFN-γ, IL-2, or IFN-α plus IL-2 [108-112]. Concurrent administration of oral dexamethasone (an immunosuppressant) and high-dose IFN-α significantly reduced the occurrence of influenza-like symptoms and fatigue in patients with advanced renal cell carcinoma [109]. Interleukin-6 induced fatigue, inactivity, and poor concentration when administered to normal subjects [113]. Neuropathic pain is a frequent complication of chemotherapy with vinca alkaloids, taxanes, and cisplatin and often persists long after treatment has ended [114]. Psychophysical studies of chemotherapy-induced

neuropathic pain demonstrated multiple zones of sensory disturbance similar to those observed in cancer and non-cancer patients experiencing pain after cytokine therapy [106,107]. Other evidence suggested that fatigue is associated with elevations in such proinflammatory cytokines as IL-1β, IL-6, TNF, and IFNs [112]. Cell types that are potential sources of cytokines and other immunoregulatory factors in cancer patients include the cancer cells themselves, [103] immune cells (neutrophils, macrophages, lymphocytes), [87,88,102,104,105] and nervous system cells (paraganglial cells, astrocytes, oligodendrocytes, microglia, and Schwann cells) [87,115,116].

Arachidonic acid metabolites and cancer

Connections between cancer and inflammation are not restricted to overlapping clinical (inflammatory) symptoms but they have much deeper, molecular foundations. For example, several reports indicate that COX-2 and 5-LOX expression may be associated with carcinogenesis most likely due to its apoptosis modulating properties [117,118]. COX-2 was shown to be upregulated in a variety of human cancers including colon, gastric, esophagus, pancreas and breast cancer, while undetectable in most normal tissues [119-124]. Furthermore, over-expression of COX-2 was sufficient to cause tumorigenesis in animal models and to render cells resistant to apoptotic stimuli [125-127].

Supporting evidence for a crucial role of COX-2 in cell survival was also provided in a COX-2 gene knock-out experiment that was done in a genetically driven mouse model of intestinal carcinogenesis. Lack of COX-2 resulted in substantial reduction in the number and size of intestinal polyps [128]. Together, these findings suggested that inhibition of the COX-2 activity, and hence the resulting decrease in prostaglandin production may contribute to the previously described anticancer effect of nonsteroidal anti-inflammatory drugs (NSAIDs) [129-131]. In addition, selective COX-2 inhibitors have been demonstrated to modulate tumorigenic, angiogenic and apoptotic events resulting in reduction of tumor incidence and progression [127].

The specific COX-2 inhibitor NS-398, for example, was shown to suppress tumor growth of different cancer cell lines and to induce apoptosis in human colon carcinoma, prostate carcinoma and esophageal adenocarcinoma cells [132-134]. Other specific COX-2 inhibitors such as nimesulide and celecoxib induced apoptosis in non-small lung cancer, prostate carcinoma, as well as colon cancer cells [135-137], and efficiently inhibited tumor growth in animal models, respectively [138]. COX-2 has therefore potential to become an attractive target for the development of novel anti-cancer strategies.

Synopsis

This short review was not designed to fully summarize our knowledge on the issues in scope (given the broadness of the topics) but rather its intention was to provide new looks and strengthen connections between inflammation, cancer, programmed (apoptotic and necrotic-like) cell death and oxidative stress, with the hope that the integrated approach will fruit development of new anticancer strategies. The interplay between inflammation, oxidative stress, apoptosis and cancer is already, to a certain extent, mirrored by the attempts of pharmacologic industry to cross-apply our current knowledge from these fields to develop new therapy approaches. For instance, strategies that modulate cellular RedOx potential are being applied to restraint inflammation (antioxidants) [139,140] or to kill cancer cells (prooxidants, e.g. carmustine, doxorubicin, paraquat) [10,141-144]. Another application of trans-disciplinary research is a trend to tap into our recent knowledge on programmed cell death for the development of novel therapies for stroke, myocardial infarction or acute and chronic inflammatory diseases [145-147].

Activation of apoptosis or attenuation of resistance of transformed cells towards cell death induction is perhaps the most promising direction chosen by many pharmaceutical companies to develop new anti-cancer drugs [148-150]. The knowledge of apoptosis can yet be used in another way in cancer therapy, eg. for cryo-conservation of hematopoetic stem cells commonly use in aggressive chemotherapy protocols [151]. As the last decade's "hype" about apoptosis research is cooling down, and our understanding of the process is mounting, more and more researchers look into modulation of cell death program so that a mixture between apoptosis and necrosis can be induced [4,5,152]. This approach has a significant therapeutic potential since necrotically-dying cells release their protein content into the surrounding tissue, thus making mutated proteins accessible for antigen presentation, recognition and (hopefully) activation of tumor-specific immune response. Induction of controlled necrosis in tumor cells, or better a mixture of necrosis and apoptosis, would have an activatory effect on the immune system [153,154]. The released tumor fragments would certainly attract the attention of primary- and adaptive immunocompetent cells, thereby contributing to the "bystander effect" and clearance of transformed cells. There is an additional optimistic aspect to of all that. Tumor cells can only become dangerous if they successfully evade both necrotic and apoptotic pathways, so reactivation of one of them may suffice to control the malignancy.

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