Necroptosis and Prostate Cancer

Subjects: Oncology

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Necroptosis is a programmed form of necrosis characterized by mitochondrial alterations and plasma membrane permeabilization resulting in the release of cytoplasmic content into extracellular space, and leading to inflammatory reactions. Besides its critical role in viral defense mechanisms and inflammatory diseases, necroptosis plays pivotal functions in the drug response of tumors, including prostate cancer. Necroptosis is mainly governed by kinase enzymes, including RIP1, RIP3, and MLKL, and conversely to apoptosis, is a caspase-independent mechanism of cell death. Numerous compounds induce necroptosis in prostate cancer models, including (i) compounds of natural origin, (ii) synthetic and semisynthetic small molecules, and (iii) selenium and selenium-based nanoparticles.

necroptosis prostate cancer RIP1 RIP3 MLKL

1. Introduction

Cell death mechanisms include accidental cell death (ACD) and regulated cell death (RCD) [1]. External extreme temperature and pressure, chemical stress, and osmotic pressure exceeding the capability of the cell to restore a physiologic condition lead to ACD. This type of cell death is an uncontrolled process in which the hallmark is the cell membrane rupturing, causing the spillover of the cytoplasm into the extracellular environment. Alterations in the cell membrane and the release of cellular content are also typical features of RCD [1][2]. RCD is controlled by molecules of specific signal cascades governing biochemical, morphological, and immunological consequences in a regulated and programmed manner. RCD guides pivotal steps of physiological and pathological processes [1]. Besides the most studied apoptosis, RCD includes autophagy, pyroptosis, ferroptosis, and necroptosis (NEC) [3][4][5][6][7][8][9]. RCD is a concept in continuous evolution. Very recently, PANoptosis, which embraces pyroptosis, apoptosis, and NEC, has emerged as a new RCD mode controlled by the aggregation of specific effector molecules leading to the formation of the PANoptosome [10][11]. The role played by PANoptosis in tumors was reported in colorectal cancer [10].

Differences in cell morphology, gene expression, and biochemical properties classify diverse forms of RCD. Therefore, molecules governing different pathways of different RCDs can be considered to be biomarkers and potential therapeutic targets [12]. The pharmacological strategy to hit selective factors of specific RCD pathways showed efficacy for cancer therapy [13]. In this context, apoptosis is paradigmatic, and the development of drugs inducing apoptosis represented the major goal of medical research [14]. However, this strategy has demonstrated numerous limits, and the emergence of drug resistance rendering tumors insensitive to apoptosis is crucial [15]. In

this scenario, the discovery of drugs that induce nonapoptotic RCD is an intriguing approach for anticancer therapy, and compounds inducing NEC in tumors, including prostate cancer (PCa), are interesting [16][17][18].

PCa is the second most diagnosed tumor (incidence of 14.1% over a total of 10.1 million new cases) and the fifth global cause of cancer death (mortality of 6.8% over a total of 5.5 million deaths) in men [19]. Men affected by localized or locally advanced PCa are treated by radical prostatectomy and radiotherapy. Conversely, metastatic androgen-sensitive PCa-suffering patients undergo androgen deprivation therapy (ADT). The disease invariably progresses towards lethal metastatic castration-resistant PCa (CRPC) that is insensitive or resistant to ADT. In spite of several efforts devised thus far in the development of new effective therapeutics on CRPC patients, including taxane-based chemotherapy (cabazitaxel and docetaxel), inhibitors of androgen synthesis (abiraterone) or signaling (enzalutamide), bone-targeting radiotherapy (radium-223) and immunotherapy (sipuleucel-T), the disease still remains lethal [20]. CRPC patients among all PCa patients, and their poor prognosis and survival reflect the need to develop other drugs. Thus, the discovery of new antitumor drugs and active medical interventions on CRPC patients is urgent, and compounds that induce NEC are expected to produce benefits [17][21].

2. Apoptosis and Necroptosis: Overview on Molecular Mechanisms

In 2005, Degterev and coworkers described NEC as a peculiar type of necrosis controlled by a specific signaling cascade that is inhibited by necrostatin 1 (Nec1) [22]. Taking advantage of a siRNA-mediated approach, receptor-interacting serine/threonine protein kinase 1 (RIP1) was identified as the target of Nec1. In 2018, such a type of programmed necrosis, not dependent on the activation of cysteine-aspartic proteases (caspases), and mainly governed by RIP1, receptor-interacting serine/threonine protein kinase 3 (RIP3) and substrate mixed lineage kinase domain like pseudokinase (MLKL) was called NEC [23]. NEC controls cell homeostasis, neurodegeneration, infectious diseases, inflammation, cardiovascular and skin diseases, acute kidney injury, and cancer [24].

Cells undergoing NEC and necrosis show similar behavior [25][26]. Although trauma, toxic stress, and infection are responsible for both necrosis and NEC, the latter differs from necrosis as a finely controlled type of RCD. Specific signaling pathways, including TNRF1 and RIP, govern NEC induction via the formation of the necroptosome complex. No important differences in morphology characterize cells undergoing NEC and necrosis (e.g., organelle and cell swelling, loss of membrane integrity, and the release of intracellular content). Moreover, both cell death mechanisms induce mitochondrial dysfunction with mitochondrial membrane collapse. However, only during NEC the production of reactive oxygen species (ROS) and the release of apoptosis-inducing factor (AIF) occur. Proinflammatory response characterizes both NEC and necrosis. Nec1 counteracts only NEC, while it is ineffective on necrosis.

Tumor necrosis factor-α (TNF-α), Fas ligand (FasL), and TNF-related apoptosis-inducing ligand (TRAIL) are death-inducing molecules acting on FasL/TNF receptor (TNFR)1, which can induce either apoptosis or NEC depending on caspase functionality (**Figure 1**) [27][28].

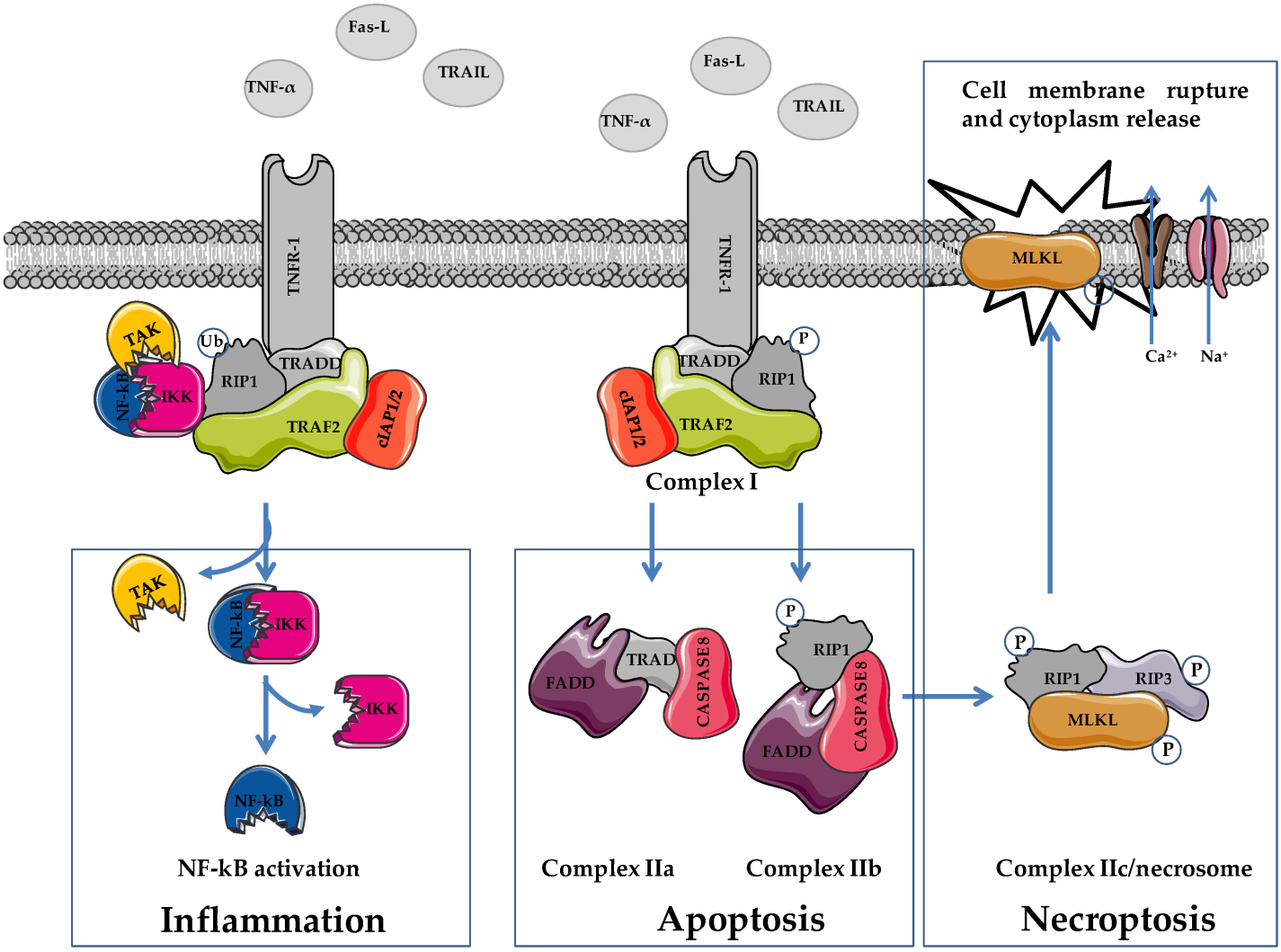


Figure 1. Schematic representation of cellular pathways involved in necroptosis. TNF-α, tumor necrosis factor α; FasL, Fas ligand; TRAIL, TNF-related apoptosis-inducing ligand; TNFR1, TNF receptor 1; RIP1/3, receptor-interacting serine/threonine-protein kinase 1/3; MLKL, mixed lineage linase domain like pseudokinase; TRADD, TNF receptor associated death domain protein; FADD, Fas-associated death domain; TRAF2, TNF receptor associated factor 2; cIAP1/2, cellular inhibitor of apoptosis proteins 1/2; TAK complex formed by TAK1, TAB2 and TAB3; IKK complex, formed by IKKα and IKKβ. Figure was prepared using tools from Servier Medical Art (http://www.servier.fr/servier-medical-art, accessed on 15 March 2022).

Cells undergoing apoptosis arrest their growth and division, and activate plasma membrane modifications, chromatin condensation, and DNA fragmentation (DNA ladder), and cell shrinkage favoring the formation of apoptotic bodies engulfing the surrounding environmental phagocytes (**Table 1**). During NEC, a cell increases its volume, and shows organelle shrinkage and plasma membrane disintegration. Cellular contents, including damage-related pattern molecules (DAMPs), high-mobility group box 1 (HMGB1), and mitochondrial DNA, are released into the extracellular environment. Conversely to apoptosis, which is characterized by limited DMAP release, the massive cytoplasm spillover observed during NEC induces an important immune response.

Table 1. Comparison of necroptosis-, necrosis-, and apoptosis-regulated cell death properties.

	Characteristic	Necroptosis	Necrosis	Apoptosis
Involved proteins	RIP3	+	/	/
	MLKL	+	/	/
	Caspase 3	/	/	+
Cell properties	Membrane perforation	+	+	/
	Membrane blebbing	/	/	+
	DNA fragmentation	+	+	+
	Cell lysis and swelling	+	+	/
	Inflammation	+	+	/

Both membrane death receptors activation (via TNF-α, TRAIL, FasL) and intracellular stimulation (via genetic damage, hypoxia, osmotic stress, or starvation) trigger apoptosis [29]. The latter, known as intrinsic (e.g., mitochondrial) apoptosis, depends on mitochondria-secreted factors including cytochrome c, SMAC/DIABLO, HrtA2/Omi, and AIF that stimulate apoptosis. Intracellular cytotoxic stimuli activate BH3-only proteins leading to BAX and BAK activation, inducing the formation of mitochondrial permeability transition pores on the outer mitochondrial membrane. This feature stimulates the release of cytochrome c into the cytoplasm and its interaction with apoptotic protease activating factor 1 (APAF1) favoring the formation of the apoptosome. This molecular complex in turn stimulates procaspase 9, 3, and 7 cleavage leading to the dysfunction or disruption of cellular components and apoptosis.

The interaction of membrane death receptors and death ligands initiates extrinsic (e.g., extracellular) apoptosis. The formation of death-included signaling complex (DISC), which contains TNFR1, Fas-FasL, death receptor 4 (DR4), death receptor 3 (DR3), and tumor necrosis factor superfamily 10 (known as TRAIL/Apo2L), is the first step of the pathway [30]. The interaction of Fas with FasL induces conformational changes of the complex that favors the exposure of Fas death effector domains, facilitating the recruitment of adaptor FADD, and the activation of procaspase 8 and 10. In turn, the cleavage or activation of procaspases 8 and 10 stimulates procaspase 3 and 7 cleavage leading to the enzymatic activation of target proteins and apoptosis [30].

Similar to apoptosis, NEC is triggered by the interaction of death receptors (Fas, TNFR1, and TNFR2) with death ligands (TNF-α, FasL, and TRAIL). In apoptosis, NEC induction requires the inhibition of caspase signaling pathways (**Figure 1**) [22][31]. The interaction of death ligands with membrane receptors provokes conformational changes that induce the recruitment of TNF receptor-associated death domain protein (TRADD), RIP1, tumor necrosis factor-related factor 2 (TRAF2), the cellular inhibitors of apoptosis cIAP1/2 and ubiquitination complex, favoring the formation of a TNFR complex (complex I) [32]. This protein complex is responsible for cell fate, i.e., death or survival, depending on the activation of downstream pathways via ubiquitination and phosphorylation activities. Through the activation of NF-kB, complex I stimulates cell survival and promotes inflammation [33][34][35]. The ubiquitination status of RIP1 favors the recruitment of transforming growth factor β kinase 1 (TAK1), TAK1-binding protein 2 (TAB2), and TAB3 (TAK complex), and the IKK complex (IKKα and IKKβ). In this condition, RIP1 functions as a scaffold protein that favors the activation of NF-kB (e.g., cIAP2-mediated degradation of NF-kB inhibitory protein Ikβ of the IKK complex), which, following nuclear translocation, stimulates cell survival (e.g., activation of antiapoptotic genes including cFLIP) and inflammation. Apart from enzymatic activity, cFLIP is highly homologous to caspase 8, and interacting with caspase 8 inhibits its activation, favoring cell survival [36][37][38][39].

The ubiquitination status of complex I elements stabilizes its localization on the cell membrane, impeding the formation of complex II and favoring cell survival [38]. Reduced RIP1 ubiquitination favors the formation and the cytoplasmic localization of complex II (IIa, IIb, and IIc/necrosome) leading to apoptosis or NEC [37][38][39]. The formation of complex IIa, which contains procaspase 8, TRADD, and FADD, allows for caspase 8 and subsequently caspase 3 activation, leading to apoptosis. The inhibition of RIP1 polyubiquitination in complex I favors its cytoplasmic localization and the interaction with FADD and procaspase 8, leading to the formation of complex IIb (RIP1/FADD/procaspase 8). Regarding complex IIa, the activation of caspase 8 induces caspase 8-dependent apoptosis as well.

Phosphorylated RIP1 (p-RIP1) interacts with RIP3 and favors its phosphorylation (p-RIP3). Following the inhibition of caspase 8 activation (e.g., via cFLIP), the p-RIP1/p-RIP3 complex recruits MLKL favoring the formation of complex IIc/necrosome. Phosphorylation on threonine 357/serine 358 of MLKL provokes its translocation on the plasma membrane leading to the activation of sodium and calcium channels, and inducing membrane dysfunction, cell rupture, and NEC execution [40][41][42].

The levels of cFLIP influence the switch apoptosis/NEC. Elevated cFLIP expression inhibits caspase 8 by forming heteromeric complex caspase 8–cFLIP, thereby blocking apoptosis dependent on complexes IIa and IIb.

Besides plasma membrane localization, the RIP1/RIP3/MLKL complex translocates to the mitochondrial membrane provoking mitochondrial dysfunction (e.g., mitochondrial permeability transition), and inducing the production of ROS and the activation of mitochondrial phosphoglycerate mutase 5 (PGAM5). Activated PGAM5 recruits mitochondrial dynamin-related protein (DRP1) leading to mitochondrial fragmentation [43]. ROS are crucial for NEC, and some evidence links RIP3 to ROS levels. RIP3 stimulates mitochondrial enzymes, including pyruvate dehydrogenase complex, glutamine synthetase, and glutamate dehydrogenase, promoting ROS production and NEC [44]. However, the involvement of mitochondria in NEC is controversial. Indeed, cells depleted of mitochondria

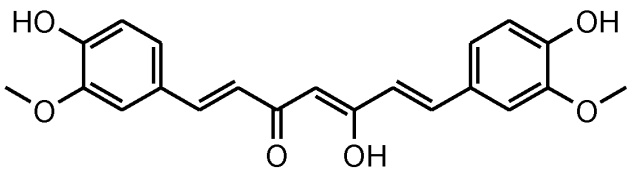
through forced mitophagy undergo NEC, implying that mitochondria or mitochondrial metabolism are not essential for this type of RCD [45]. This scenario reveals that the kinase-dependent NEC can be viewed as a rescue mechanism of cell death functioning when caspase-mediated apoptosis fails [26][40][46].

3. Necroptosis and Necroptosis Inducers in Prostate Cancer

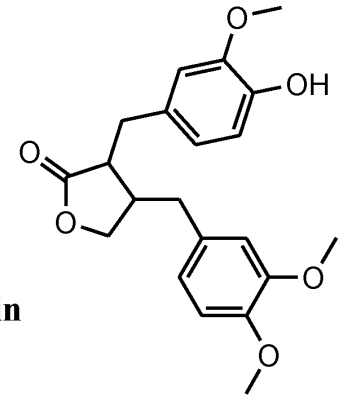
Though reported since 2005, the induction of NEC for fighting PCa is still scarcely considered. RIP3 is decreased in PCa specimens and in cell lines (e.g., PC3, DU145, and 22Rv1). Moreover, in advanced PCa samples, RIP3 is significantly downregulated compared to normal tissue [47]. The reduced expression of RIP3 correlates with tumor size and prostate-specific antigen (PSA) levels [48]. High or normal levels of RIP3 counteract disease progression by favoring MLKL phosphorylation, leading to NEC. The overexpression of RIP3 in PC3 and 22Rv1 cell lines induces G2 cell-cycle arrest, reduces cell survival, proliferation, invasion (increased MMP2 and MMP9, vimentin, fibronectin, and N-cadherin), and favors NEC (phosphorylation of MLKL) [47]. In addition, compared to corresponding parental tumors, tumorigenesis and tumor volume are reduced in mice bearing RIP3-overexpressing PC3 and 22Rv1 tumors [47].

The seven members' sirtuin (SIRT) family of proteins shows enzymatic activity implicated in numerous cellular functions, including DNA damage repair, senescence, metabolism, and tumor development and progression. Two enzymes of this family, SIRT3 and SIRT6, are involved in NEC induction in PCa. The increased expression of SIRT3 and SIRT6 is significantly associated with nodal metastasis and Gleason score, and negatively impacts on overall patient survival [49]. Therefore, the silencing of SIRT3 and SIRT6 in LNCaP, DU145, and PC3 cells significantly reduces cell growth, which is paralleled by RIP3-mediated NEC induction (e.g., increased phosphorylation of RIP3 and MLKL). These results were confirmed in vivo in SIRT3 and SIRT6 silenced LNCaP tumor xenografts that showed reduced tumor volume compared to the corresponding tumors expressing normal enzyme levels.

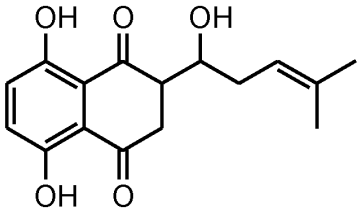
Compounds that induce NEC are receiving considerable attention, and several molecules, though not specific NEC inducers, showed antitumor activity on PCa cell lines (**Figure 2** and **Figure 3**). Available compounds are: (i) of natural origin, (ii) synthetic and semisynthetic small molecules, and (iii) selenium and selenium-based nanoparticles (SeNPs).



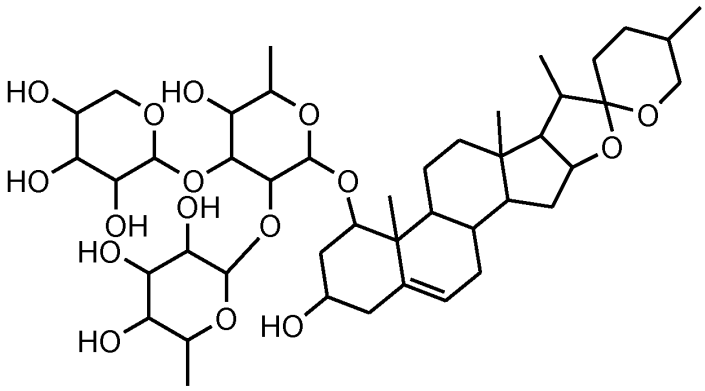
Curcumin



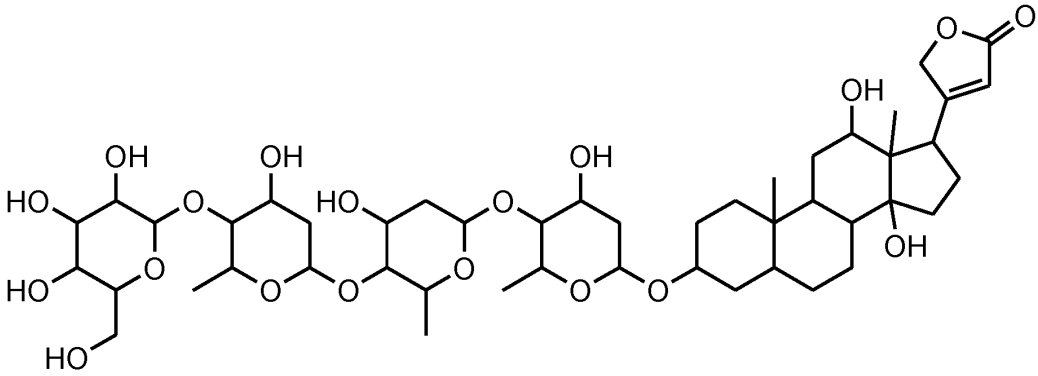
Arctigenin



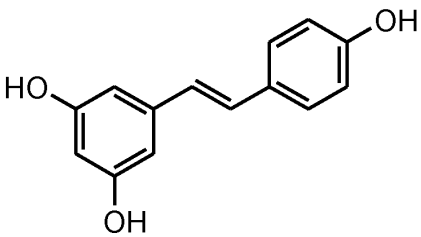
Shikonin



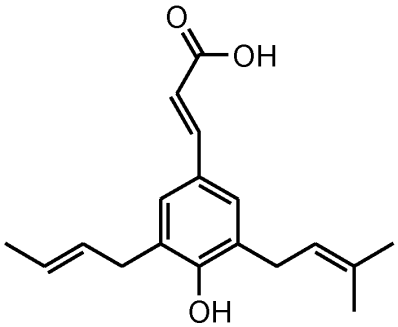
Ophiopogonin D



Deslanoside



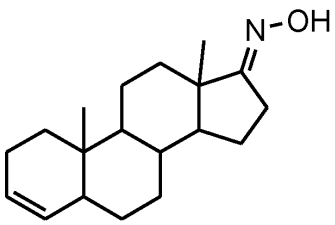
Resveratrol



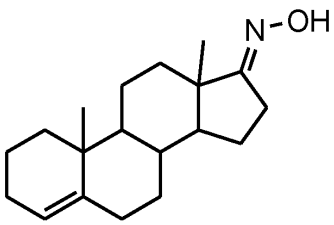
Artepillin C

Resveratrol Artepillin C

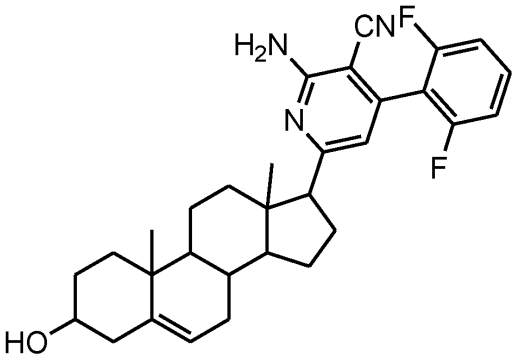
Figure 2. Chemical structures of compounds of natural origin that induce necroptosis in prostate cancer cell lines. These compounds stimulate necroptosis by inducing (i) the dysfunction of mitochondrial membrane potential, curcumin, and arctigenin; (ii) cell-cycle arrest, shikonin; (iii) FADD stabilization, ophiopogonin D'; (iv) modulation of multiple necroptosis pathways, deslanoside; (v) reactive oxygen species, resveratrol; (vi) RIP1/3 activation following combination with autophagy inhibitors, artepillin C.



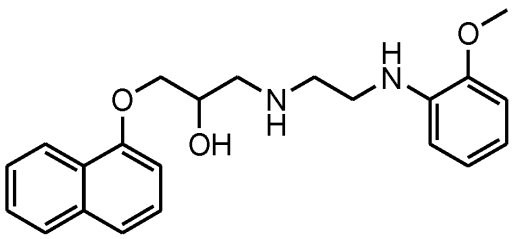
(17E)-5alpha-androst-3-en-17-one oxime



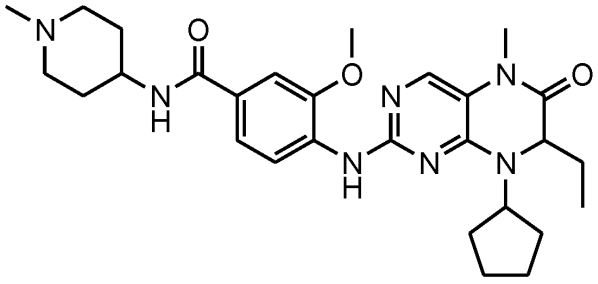
(17E)-5alpha-androst-4-en-17-one oxime



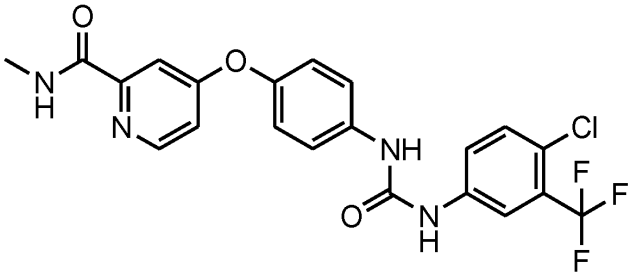
17-Cyanopyridine pregnenolone



Naftopidil derivative (HUHS1015)



BI2536



Sorafenib

Figure 3. Chemical structures of synthetic and semisynthetic small molecules that induce necroptosis in prostate cancer cell lines. These compounds stimulate necroptosis by (i) inducing mitochondrial membrane permeability, (17E)-5α-androst-3-en-17-one oxime and (17E)-androst-4-en-17-one oxime; (ii) inducing reactive oxygen species

and cell-cycle arrest, 17-cyanopyridine pregnenolone; (iii) inducing cell growth inhibition following combination with necrostatin, HUHS1015; (iv) inhibiting Polo-like kinase 1, BI2536; (v) inhibiting kinases, sorafenib.

4. Ongoing Clinical Trials Containing Necroptosis Inducers in Prostate Cancer

Some compounds reported here are contained in clinical trials enrolling patients suffering from PCa (**Table 2**, www.clinicaltrials.gov, accessed on 23 February 2022).

Table 2. Clinical trials containing necroptosis inducers ongoing in prostate cancer [a].

Compound	NCT Number	Markers	Phase
Curcumin	NCT03769766	PSA	III
	NCT03211104	PSA	na
	NCT02064673	PSA	III
Curcumin and piperine	NCT04731844	nd	II
Curcumin and ursolic acid	NCT04403568	p65, NF-kB	I
Curcumin and Vitamin D, omega 3, turmeric	NCT03290417	PSA	na
Curcumin and taxotere	NCT02095717	PSA	III
Curcumin and radiotherapy	NCT01917890	TNF-α, NF-kB	na
	NCT02724618	PSA	II
	NCT03493997	nd	II

Compound	NCT Number	Markers	Phase
Polyphenon E	NCT00596011	PSA	II
	NCT00676780	PSA, VEGF, HGF	II
	NCT01340599	PSA, Ki67, Bcl2, Cyclin D, p27, VEGF, CD31, MMP2 and 9, IGF1	II
	NCT00459407	MMP2, MMP9, IGF1	I
	NCT00253643	FASN, Ki67	na
	NCT04597359	PSA, Ki67	II
BI2536	NCT00706498	PSA	II
Sorafenib	NCT00090545	PSA	II
	NCT00694291	PSA	II
	NCT00466752	PSA, p-ERK, p-AKT, p-S6-kinase, caspase 3, Ki67	I
	NCT00093457	PSA	II
Sorafenib and leuprolide or bicalutamide	NCT00924807	PSA	I-II
Sorafenib and docetaxel	NCT00589420	PSA	II

Compound	NCT Number	Markers	Phase
	NCT00619996	PSA, p-ERK, VEGF-R2	II
Sorafenib and taxotere	NCT00405210	PSA	I
Sorafenib and mitoxantrone	NCT00452387	PSA	II
Sorafenib and gleevec	NCT00424385	PSA	I
Selenite and docetaxel	NCT01155791	PSA	I
Selenite and radiotherapy	NCT02184533	PSA	I

[a] altrial.gov

ation with turmeric phase II; omarkers, 01917890 y are not specific biomarkers.

Polyphenon E was included in numerous studies as supplementary diet in subjects at high risk of developing PCa (prostatic hyperplasia) or in postsurgery patients (NCT00596011, phase II; NCT00676780, phase II; NCT01340599, phase II; NCT00459407, phase I; NCT00253643; NCT04597359, phase II). Polyphenon E-based studies contemplated the measure of numerous biological markers (e.g., PSA, Ki67, Bcl2, Cyclin D, p27, VEGF, CD31, MMP2 and 9, IGF1, HGF, FASN) but not specifically related to NEC.

Sorafenib alone (NCT00090545, phase II; NCT00694291, phase II; NCT00466752, phase I; NCT00093457, phase II) or in combination with leuprolide acetate or bicalutamide (NCT00924807, phase I-II), docetaxel (NCT00589420, phase II; NCT00619996, phase II), taxotere (NCT00405210, phase I) mitoxantrone (NCT00452387, phase II) or gleevec (NCT00424385, phase I) is investigated in PCa patients. In all these studies, PSA is used as biological marker. The trial NCT00619996 contemplates the measure of p-ERK and VEGF-R2 as well. Interestingly, in trial NCT00466752, samples from PCa patients collected before and after sorafenib administration were analyzed for gene and protein expression by microarray, Western blot, and immunohistochemistry. In this context, the levels of p-ERK, p-AKT, p-S6- kinase and caspase-3 expression, and the Ki67 index were considered. Though the study is completed, results are not yet available. In sorafenib-containing clinical trials, specific biomarkers of NEC are also not measured.

Selenite in combination with docetaxel (NCT01155791, phase I) or with radiotherapy (NCT02184533, phase I) is studied in PCa-affected patients. In these studies, PSA was the only considered biomarker.

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