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The role of Nr1d1 in tumor

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Abstract: REV-ERB receptor is a member of protein nuclear receptor superfamily, which is both intracellular receptor and transcription factor, so it regulates the expression of target gene. REV-ERB acts as a transcription inhibitor because of its unique structure. Their main function is to control the peripheral circadian rhythm by participating in the transcription-translation feedback loop with other major clock genes. As for their role in the pathogenesis of cancer, recent studies in various cancer tissues show that their expression is down-regulated in most cases. The imbalance of its expression is also related to cancer-related cachexia. The use of synthetic agonists can restore its pharmacological significance. Synthetic agonists have been explored in preclinical studies, but the data are scarce. It is necessary to further study, mainly through the mechanism study, the influence of REV-ERB-induced circadian rhythm disorder on carcinogenesis and cancer-related systemic effects (such as cachexia), in order to solve the potential problems of related therapeutic significance.

1. Introduction

Group 1 D member 1 of nuclear receptor subfamily (NR1D1, also known as REV-ERBα) belongs to the nuclear receptor (NR) family, and is a heme binding component that consolidates the biological clock of circadian oscillator. In addition to inhibiting the transcription of several clock genes related to circadian rhythm, NR1D1 also has a wide range of downstream target genes, which are closely related to many physiological and pathological processes, including autophagy, immunity, inflammation, metabolism and aging of multiple organs. This paper focuses on the key role of NR1D1 as a key transcription factor in gene regulatory network, and especially emphasizes the milestone of the latest discovery of NR1D1 ligand. NR1D1 is considered as a promising drug target for the treatment of many diseases, which may contribute to the research of innovative biomarkers and therapeutic targets for cancer-related diseases. Further study of NR1D1 ligand in prospective human trials may pave the way for its clinical application in many cancer-related diseases.

2. Background

Group 1 D member 1 of nuclear receptor subfamily (NR1D1, also known as REV-ERBα) was first discovered in 1989. It is a protein of about 56 kD, which is encoded by the reverse DNA strand of ERBA (also known as THRA) oncogene. In 1994, a new orphan receptor was successfully found in many laboratories, which has high homology with the rat REV-ERBα gene product (especially in the DNA binding domain and ligand binding domain), and is called NR1D2 or REV-ERBβ. NR1D1 and NR1D2 are key transcription inhibitors of regulatory networks with circadian rhythm expression

patterns, which are widely expressed in many tissues.

NR1D1 can bind to promoters of many genes, and mediate transcription inhibition of important participants in physiological and pathological processes of various organs, such as autophagy-related proteins, inflammatory corpuscles genes, T cell differentiation cofactors, lipid metabolism enzymes, etc. Molecularly, NR1D1 inhibits the transcription of RNA(eRNA) derived from the enhancer and reduces the mRNA expression of the target gene by recruiting the nuclear receptor co-repressor (NCOR)- histone deacetylase 3(HDAC3) complex to the enhancer or promoter of the target gene.

This review studies the latest discovery milestone of NR1D1 in many physiological and pathological processes of cancer cells. According to NR1D1' s involvement in autophagy, immunity, inflammation, aging and metabolism, researchers have identified and designed a variety of natural and synthetic NR1D1 ligands, which can stimulate or block intrinsic signal transduction. These agonists and antagonists are usually small synthetic compounds, and some of them have entered the pre-clinical trial stage. Therefore, NR1D1 is considered as a prospective pharmacological target of many diseases, which may help to provide new insights for the treatment strategy of organ injury.

3. Structure and action form of 3.Nr1d1

NR1D1 and NR1D2 belong to the nuclear receptor (NR) subfamily, but their structures are slightly different from those of classical nuclear receptors. There are four main domains in NR that can distinguish typical nuclear hormone receptors: variable amino N-terminal activation function 1(AF-1), highly conserved DNA binding domain (DBD) composed of two zinc finger motifs, hinge region connecting DBD to carboxyl terminal ligand binding domain (LBD), and conserved LBD that mediates the interaction of co-activators through the absence or presence of regulatory AF-2 region LBD. DBD is targeting receptors to some so-called hormone response elements. In addition to the hinge region and LBD, DBD also participates in the dimerization of NR with its partner. In addition, LBD promotes ligand-dependent interaction with transcription co-activators or co-inhibitors through conformational changes. After binding the ligand, LBD allows the receptor to switch to the transcriptional active state. It also has the key characteristics of hormone recognition and controls the selectivity and specificity of physiological response. These semisites are arranged as palindromes or direct repeats. The carboxyl-terminal helical AF-2 fragment can recognize the co-activating factors necessary for transcriptional activation, and it is very important for ligand-dependent recruitment of co-activating factors and transcriptional activation of NRs. Notably, NR1D1 and NR1D2 lack AF-2 region, so they are considered unable to activate transcription. Therefore, they are indeed constitutive transcription inhibitors, which control the transcription of genetic information by binding to specific DNA sequences.

NR1D1 has two main forms of inhibiting transcription, namely monomer and homodimer. NR1D1 usually binds to thyroid/retinoic acid receptor half-site AGGTCA as a monomer, flanked by A/T-rich sequence 5'. This half-site is located in the promoter of the target gene and is called Rore/Rev-Erb-response element (RORE/RevRE). In 1998, Zhao et al. revealed that the interaction between the A/T-rich 5' extension of AGGTCA semi-site and the C-terminal extension of DBD enhanced their high affinity. In addition, NR1D1, as a homodimer, binds to a tandem repeat at the Rev monomer site ("DR2") with an interval of 2 bp, while the A/T-rich sequence is flanked by the 5' half site of DR2. Therefore, the sequence is called RevDR2. Compared with the binding of NR1D1 monomer and Rev monomer, the stability of this interaction is 5-10 times higher. In some cases, two NR1D1 molecules can be linked to two nearby RORE separately, and co-inhibitory factors (NCOR1-HDAC3) can be recruited to inhibit gene transcription.

Since the eighteenth century, the research on the mechanism of biological clock has been going on. Konopka and others initially studied the biological clock gene with Drosophila as a model, and

found the biological clock gene in Drosophila mutant. There is a central "master" clock in the suprachiasmatic nucleus (SCN) of mammalian hypothalamus, which integrates the information from light and synchronizes our physiological functions with the circadian cycle. In fact, many rhythmic activities are mediated by peripheral oscillators in various tissues and cells, and the central clock in the brain coordinates various rhythmic activities in different tissues.

Circadian rhythm is a 24-hour behavior and circadian rhythm generated by biological clocks found in many species. In mammals, the biological clock is located in SCN. On the one hand, the main pacemaker in SCN receives the main entrainment signal from the ambient light-dark cycle. On the other hand, it maintains the synchronous rhythm of behavior and physiology in cells and tissues by aligning the circadian rhythm gene oscillation in neurons outside SCN and peripheral tissues. Almost all physiological functions are regulated by biological clock, and disorder has serious adverse effects on health. The most important mechanism by which circadian rhythm can last for about 24 hours is the transcription-translation feedback loop (TTFL) of biological clock. The internal clock consists of many genes and their encoded protein, such as brain and muscle ARNT-like 1(BMAL1), circadian movement output cycle kaput(CLOCK), cycle (PER), CRYptochrome (cry), Nr1d1 and RAR-related orphan receptor α(RORα), all of which affect different physiological processes in the body through TTFL. The central molecular circadian oscillator loop is composed of BMAL1/CLOCK heterodimer. In mammals, CLOCK and BMAL1 interact with the E-box of Per and Cry promoter regions, triggering the transcription of these two genes in the nucleus. These genes were then translated into target proteins PER1-3 and CRY1-2 in cytoplasm. On the contrary, PER1-3 and CRY1-2 can inhibit the transcription of CLOCK and BMAL1, forming a negative feedback loop. Importantly, many clock control genes (CCG) are located downstream of these four components and coordinate the oscillation of various physiological functions. Nuclear receptors REV-ERB and ROR form a second feedback loop. The daily oscillation of Rev-erbs transcription is caused by the combination of CLOCK/BMAL and E-box of promoter. Nr1d1 is the main inhibitor of Bmal1 transcription, and RORα is the activator of transcription. These two factors compete to bind the RORE/RevRE site located in the Bmal1 promoter, and then regulate the transcription of Bmal1 and RORE/RevRE control gene (RCG). Therefore, Nr1d1 and RORα participate in the regulation circuit, which is very important for the proper timing of the kernel clock mechanism and the occupation of Bmal1 promoter. In the third loop, PER2 (the output gene product from the main loop) and D-box control gene (DCG) are influenced by DBP and E4 promoter binding protein 4(E4BP4).

Although the patterns are different, all clock genes are expressed periodically. It is worth noting that many clock control genes (CCG), such as Bmal1 and E4bp4, are controlled by NR1D1 and show different patterns from NR1D1. Therefore, NR1D1 is a transcription inhibitor and one of the key participants in controlling the negative feedback mechanism of biological clock.

4. The role of NR1D1 in various cancers

The role of NR1D1 in various cancers In order to further develop and form metastasis in organisms, cancer cells must escape a series of protective mechanisms, leading to the failure of several key cell functions from apoptosis to DNA damage, which are called the signs of cancer. Recent research shows that several (if not all) of these signs are controlled by circadian rhythm. In mammals, up to 80% of protein coding genes are clock-controlled, and expressed in at least one tissue in a circadian rhythm. Therefore, the disorder of biological clock will affect cell homeostasis and may make individuals susceptible to cancer.

4.1. Nr1d1 in breast cancer

Breast cancer is the most commonly diagnosed cancer among women in the world, and it is also

the main cause of cancer-related death. Interferon gene stimulating factor (STING) pathway is very important for inducing type I interferon to trigger anti-tumor immunity. Induction of cytoplasmic DNA by cyclic guanosine monophosphate synthase (cGAS) leads to the activation of STING and downstream signal molecules, including tank-binding kinase 1 (TBK1) and IFN regulatory factor 3 (IRF3). In turn, these will lead to increased expression of type I IFN and downstream chemokines, such as CC chemokine ligand 5 (CCL5) and C-X-C motif chemokine ligand 10 (CXCL10). Thereby inducing cytotoxic T cells and natural killer (NK) cells to infiltrate and activate to the tumor site. Nr1d1 inhibits DNA repair in breast cancer cells by binding DSB sites, thus inhibiting the further recruitment of DDR factors. At the same time, Na-Lee Ka and others found that the growth and lung metastasis of breast cancer will be enhanced when NR1D1 is knocked out. It also shows that NR1D1 activates type I IFN reaction through cGAS-STING signal transduction induced by cytoplasmic DNA, and NR1D1 agonists GSK4112 and SR9009 can activate type I IFN signal transduction, thus inducing anti-tumor immunity in vitro and in vivo [1].

4.2. Nr1d1 in renal cell carcinoma

Renal cell carcinoma (RCC) is a common malignant tumor with high morbidity and poor prognosis. A study on the prognosis of RCC showed that the circadian rhythm of 13 rhythm genes changed in the kidney tissue of mice, and the expression and methylation level of NR1D1 in cancer cells increased [2]. This discovery shows that the circadian rhythm has a significant influence on RCC, and provides a solid foundation for the diagnosis, prognosis and drug suggestion of RCC in the future.

4.3. Nr1d1 in gastric cancer

Gastric cancer is the fifth most common malignant tumor, causing more than 770,000 deaths worldwide every year. Xiaoshan Wang et al found that the expression level of Nr1d1 was down-regulated in GC, and the PFS (progression-free survival) time of patients with high expression level of Nr1d1 was longer than that of patients with low expression level of Nr1d1 [3].

4.4. Nr1d1 in colon cancer

Colorectal cancer (CRC) is one of the three most common malignant tumors and one of the most deadly cancers in the world. MACC1 plays an important role in the process of tissue cells transforming from benign to malignant. With the increasing expression of MACC1, the ability of distant metastasis of tumor tissues will be stronger. Alireza Basti and others found that there was an interaction between MACC1 and biological clock, and circadian rhythm played an important role in regulating the proliferation and metastasis of CRC cells [4]. Therefore, these findings may be beneficial to the treatment of CRC, especially when targeting MACC1 and/or clock components in patients.

4.5. Nr1d1 in lung cancer

Lung cancer is one of the most common cancers with a high mortality rate, accounting for 18% of cancer-related deaths in 2020. Sun Mi Kim et al. found that the lack of Nr1d1 in mice promoted the development of lung tumor and NR1D1 had tumor inhibition in TME. [5] In addition, recent studies have shown that NLRP3 inflammatory corpuscles are related to the tumorigenesis of various cancers. Although the role of NLRP3 inflammatory corpuscles in tumorigenesis is still controversial, most studies have shown that NLRP3 inflammatory corpuscles can promote tumorigenesis. However, Sun Mi Kim and others have also proved that NR1D1 plays an anti-oncogene role in lung cancer by

negatively regulating NLRP3 inflammatory corpuscles.

4.6. Nr1d1 in Bladder Cancer

Bladder cancer (BC) is one of the most common malignant tumors in urinary system, with about 550,000 newly diagnosed cases and 200,000 deaths worldwide every year. Yubo Yang et al. found that the down-regulation of Nr1d1 is related to the poor prognosis of BC, and proved that the over-expression of NR1D1 can inhibit the growth and function of BC cells [6]. Therefore, NR1D1 acts as a tumor suppressor gene and may become a new target for the treatment of BC.

4.7. Nr1d1 in Ovarian Cancer

Ovarian cancer is one of the most common gynecological malignant tumors in the world. It is estimated that there were 22,240 new cases and 14,070 deaths of ovarian cancer in the United States in 2018. Huailin Wang et al. found that the up-regulation of NR1D1 inhibited the proliferation of ovarian cancer cells and induced cell cycle arrest and apoptosis, while silencing NR1D1 promoted the proliferation and G1/S transformation of ovarian cancer cells. In addition, NR1D1 inhibited JAK/STAT3 signaling pathway, which is closely related to cancer progression. Consistent, the growth rate of xenografts overexpressed by NR1D1 in vivo was slower than that of the control group. In addition, NR1D1 upregulated the expression of cytokine signal transduction inhibitor 3 (SOCS3), which is an inhibitor of JAK/STAT3 signaling pathway [7]. This study emphasizes the far-reaching role of NR1D1 in the treatment of ovarian cancer.

5. Overview of Nr1d1 Ligands

Nr1d1 is a nuclear receptor that can be targeted by small molecular ligands. Burris and his colleagues conducted an excellent review of REV-ERB ligands in 2014. In recent years, a series of new Nr1d1 ligands have been discovered, most of which have pharmacological activities in vivo. In the following sections, we will introduce the newly discovered ligands and old ligands and their targeting potential.

5.1. Haemoglobin

Heme was identified as the endogenous ligand (agonist) of REV-ERB in 2007. Heme binds to the ligand-binding pocket of REV-ERB by interacting with two residues (histidine on helix 11 and cysteine on helix 3). In addition, a large number of hydrophobic residues in the ligand-binding pocket form hydrophobic interactions with the porphyrin ring of heme molecule. As a prototype agonist, Heme has been used to verify the effect of REV-ERB activation on gene expression in vitro. Manipulating heme homeostasis has been proved to change circadian rhythm gene expression and glucose metabolism, highlighting the role of heme and REV-ERB in circadian rhythm biology.

5.2. GSK4112

The discovery of heme as REV-ERB ligand opens the door for developing more effective synthetic ligands. GSK4112 (also known as SR6472) is the first synthetic ligand for REV-ERB, which was identified by fluorescence resonance energy transfer (FRET) assay. GSK4112 has been used as an in vitro probe for Nr1d1 function. Please note that GSK4112 is not suitable for detecting the function of Nr1d1 in vivo due to low system exposure (poor pharmacokinetics). GSK4112 activates Nr1d1 to inhibit NF-κB signaling and the activity of inflammatory corpuscles of NLRP3, thus preventing the

production of cytokines and chemokines, indicating that Nr1d1 has anti-inflammatory effect. GSK4112 reduces the activity of 3T3-L1 preadipocytes and the expression of cyclin D (a proliferation-related gene) and β-catenin, revealing the role of Nr1d1 in cell proliferation and apoptosis. In addition, GSK.

5.3. SR8278

SR8278 is the first synthetic antagonist of REV-ERB. Based on Gal4 co-transfection and luciferase reporter gene assay, SR8278 inhibits the transcriptional inhibitory activity of REV-ERB in a dose-dependent manner. However, its pharmacokinetics is poor and its elimination half-life is short, about 0.17 hours. SR8278 is widely used to detect the function of REV-ERBs in vitro. SR8278 induces the expression of Myogenic genes (Myod, myog and Mhc3) in the proliferation and differentiation of myoblasts, indicating the regulatory role of REV-ERB in myogenesis. The antagonism of SR8278 to REV-ERB increases the intracellular lactic acid level (reduces glycolysis) in SGC-7901 and BGC-823 cells. SR8278 has also been tried for many times in vivo. SR8278 decreased the homocysteine levels in plasma and liver of mice, which indicated that hyperhomocysteinemia was relieved by Nr1d1 antagonism. SR8278 increased lean body mass and improved muscle function of malnourished mice by activating Wnt signal transduction.

5.4. SR9009 and SR9011

SR9009 and SR9011 are two effective REV-ERBs agonists designed based on the chemical structure of GSK4112. The efficacy and effectiveness of these two compounds are about three times that of GSK4112, and they show better pharmacokinetic characteristics (which may be suitable for in vivo research). In addition, their exclusive effect on REV-ERB (no effect on other 46 nuclear receptors) has been confirmed by Gal4 chimeric assay. Therefore, SR9009 and SR9011 have been widely used to test the effects of REV-ERB on rhythmic behavior and diseases in vitro and in vivo.

The specific effects of SR9009 and SR9011 on REV-ERB were also supported by the study of functional loss in Nr1d1-deficient mice. SR9009 alleviated DSS-induced colitis and myocardial ischemia-reperfusion in wild-type mice, but failed to do so in Nr1d1-deficient mice, indicating that the effects of SR9009 were Nr1d1-dependent. However, two groups of researchers reported the potential off-target effects of SR9009 and SR9011. These two agonists showed some LXR activity in Trump et al. SR9009 and SR9011 replaced radioactive ligands from LXRα binding site, and SR9011 increased ABCA1 (a LXR target gene) mRNA in THP-1 cells. In Dierickx et al.' s research, the exact mechanism of REV-ERB-independent effects of SR9009 on the proliferation, metabolism and gene transcription of mESC and hepatocytes with REV-ERB deficiency is still unknown.

5.5. GSK2945

GSK2945 was also designed based on GSK4112 scaffold, but it showed superior pharmacokinetic characteristics, with a longer half-life of 2.0 hours and an oral bioavailability of 23%. The compound inhibited the activity of luciferase reporter gene driven by BMAL1 promoter in U2OS cells in a dose-dependent manner, indicating that it had an exciting effect on REV-ERB. However, Zhang et al reported that, In Gal4 chimera assay, GSK2945 antagonized the inhibitory activity of Nr1d1 in a dose-dependent manner. GSK2945 also inhibited the activity of Bmal1 reporter gene and blocked the excitatory activity of GSK4112. In addition, the authors proved that GSK2945 increased the mRNA expression of BMAL1 and PECK (two known target genes of REV-ERB) in HepG2 cells and hepatocytes, as well as in mice. So far, GSK2945 has been used to detect the expression of BMAl1 and PECK. The effect of GSK2945 may be cell/tissue specific, because the activity of REV-ERB

may be influenced by the cell microenvironment (such as redox state, small molecular gas and cofactor type). Modification of ligand-bound REV-ERB by redox conditions and gas may lead to ligand transformation.

5.6. ARN5187

ARN5187 directly interacts with the LBD of REV-ERBβ and acts as an antagonist. ARN5187 induces the activity of the luciferase reporter gene driven by RORE in a concentration-dependent manner, and this effect will be lost when RORE mutates. In addition, ARN5187 is a dual inhibitor of REV-ERB and autophagy. The application of this dual inhibitor may be an effective strategy to induce cancer cell toxicity.

5.7. Chelidonic acid and bilirubin

Hering et al. used a cell-based two-hybrid assay system to identify chelating acid as an agonist of Nr1d1. Leucine specifically binds to the LBD site of Nr1d1, resulting in enhanced binding between Nr1d1 and the co-repressor protein NcoR1. Wang et al. identified bilirubin, a catabolite of heme, as an antagonist of Nr1d1 based on Gal4 co-transfection and Bmal1 luciferase reporter gene assay. Although related in structure, bilirubin and heme showed opposite effects on REV-ERB (i.e. antagonist and agonist). Other structurally related compounds (for example, SR8278 and GSK4112; Cobalt protoporphyrin IX and heme have similar findings.

5.8. GSK1362

Pariollaud et al. developed a new selective oxazole inverse agonist for REV-ERB, named GSK1362. According to FRET assay, GSK1362 inhibited the interaction between Nr1d1 and NCoR1 and SMRT2 peptides. It also increased the activity of luciferase reporter gene driven by Bmal1 promoter in HEK293 cells in a dose-dependent manner. In addition, the model of binding between GSK1362 and Nr1d1 was established by cell thermal displacement measurement, and it was proved that the O- methyl ethanolamine side chain of oxazole (which formed a key hydrogen bond with Lys473) was very important for the activity of the compound. Notably, GSK1362 does not induce the expression of Abca1 and Abcg1 (two known LXR target genes), indicating that it has no effect on LXR receptor. Surprisingly, GSK1362 inhibits LPS-induced Il-6 in bone marrow-derived macrophages like REV-ERB agonist, thus increasing the possibility of off-target effect.

5.9. SR12418

Amir et al. synthesized the specific synthetic ligand of REV-ERB by modifying the chemical structure of SR9009 (named SR12418).SR12418 was bound to REV-ERBs according to the time-resolved fluorescence resonance energy transfer assay, and showed the exclusive effect based on Gal4 chimeric assay. It can effectively inhibit the activity of Bmal1- luciferase reporter gene by IC, which is less than one tenth of that of SR9009 (68 nM for SR12418 and 710 nM for SR9009). SR12418 is more effective than SR9009 in inhibiting REV-ERB target gene (such as IL-17). In addition, SR12418 showed better pharmacokinetic characteristics than SR9009. It has been used as a probe in vivo to examine the pharmacological effects of REV-ERB on experimental autoimmune encephalomyelitis and colitis.

5.10. Berberine and puerarin

It is reported that berberine (originally isolated from the root nodule of Coptis chinensis) is an agonist of Nr1d1, based on three evidences. Firstly, berberine inhibits the activity of Bmal1-luciferase and Nlrp3- luciferase reporter genes. Secondly, berberine enhanced the activity of Nr1d1 repressor protein in Gal4 co-transfection experiment. Thirdly, the treatment of bone marrow-derived macrophages with berberine leads to the decrease of the expression of Nr1d1 target gene. Puerarin is isolated from Pueraria lobata, which is a traditional Chinese medicine widely used to treat fever, vomiting, diarrhea, cardiac insufficiency and liver injury. Chen et al. found Puerarin as an antagonist of Nr1d1, based on luciferase reporter gene, Gal4 co-transfection and target gene expression determination. Berberine and Puerarin are quite different from other synthetic ligands in chemical structure, indicating that a new chemical scaffold for Nr1d1 ligand has been found. However, the selectivity of berberine and puerarin to REV-ERB has not been verified.

5.11. Other ligands

GSK0999, GSK5072 and GSK2667 were identified together with GSK2945 in the same study. These three compounds showed similar pharmacokinetic characteristics to SR9009. In addition, they have no effect on LXRα. ENA_T5382514, ENA_T5445822 and ENA_T5603164 were identified as REV-ERB ligands in large-scale screening of 29568 different compounds from Enamine compound library. ENA_T5382514 and ENA_T5445822 are agonists, while ENA_T5603164 is antagonist. However, all three compounds are related to off-target effect (for example, their effects on xenobiotic nuclear receptors such as CAR and PXR).

6. Conclusion

Nr1d1 is a nuclear receptor that acts as a transcription inhibitor related to biological clock, and together with other essential clock genes, it becomes a part of an important transcription-translation feedback loop. Recent studies have explored their role in the pathogenesis of cancer. In most studies, it is found that they are down-regulated in human cancer tissues and preclinical cancer models, and their down-regulation is related to cell proliferation in cancer cell lines. The use of synthetic agonists can restore its pharmacological significance. Synthetic agonists have been explored in preclinical studies, but the data are scarce. Drug development and clinical transformation in this field are challenging, and it is necessary to better characterize Nr1d1 disorder and its association with specific malignant phenotype. In addition, targeting Nr1d1 receptors can be used to "time-regulate" other anticancer drugs and optimize their results. It is necessary to further study the influence of circadian rhythm disorder induced by Nr1d1 on carcinogenesis and cancer-related systemic effects (such as cachexia) in order to solve the potential problems of related therapeutic significance.

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