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Review

Hyperthermic Cancer Therapy Combined with Inhibitors Targeted Against Heat-induced Signaling Factors

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Abstract: In this review, we summarize the molecular mechanisms of chemical inhibitors and small interference RNAs (siRNAs) specifically targeted against signaling factors involving in heat-induced signal transduction pathways for anti-apoptosis/cellular proliferation and DNA repair. Since there are still few reports of the chemical inhibitors and siRNAs with respect to sensitization to heat, the effective chemical inhibitors and siRNAs which block the signal transduction pathways are required from an aspect of fundamental research. We expect the attractive sensitizers described here to contribute to high curative efficiency in hyperthermic cancer therapy.

Key words: apoptosis, heat, hyperthermia, inhibitor, siRNA

Introduction

Hyperthermia has been developed as one of the efficacious cancer therapies ¹ ². To develop more efficient regimens for treating various malignant tumors, useful agents that sensitize cancer cells to hyperthermia are still strongly required. Inhibitors which interfere with anti-apoptosis/cellular proliferation signal transductions are now being developed to enhance heat-induced cell killing.

Recent molecular biological studies have addressed the heat-induced signal transduction pathways for apoptosis. Apoptosis is a beneficial physiological response resulting in cell death without inflammation. Heat-induced apoptosis has been reported to be induced through p53-centered ³ and/or c-Jun N-terminal kinase (JNK)-centered signal transduction ⁴ ⁵. On the other hand, heat activates signal transduction pathways not only for apoptosis but also for anti-apoptosis/cellular proliferation. Several signaling factors, such as Akt, p38, extracellular signal-regulated kinase (ERK) and heat shock protein (HSP), play important roles in anti-apoptosis/cellular proliferation pathway. Such signaling factor-related pathways are disadvantageous to hyperthermic cancer therapy. Therefore, targeted inhibition of such signaling factors is useful for the development of potent hyperthermic cancer therapy. It is worth notice that Trastuzumab and ZD1839 (also called Herceptin and Iressa, respectively) that inhibit anti-apoptosis/cellular proliferation pathways have caused good outcomes in breast and lung
RNA interference (RNAi) has become a useful tool for selective suppression of targeted gene expression to clarify the molecular mechanisms of the expression of various genes. Based on its mechanism of action, RNAi has been applied for the enhancement of radiosensitivity or chemosensitivity of cells. Application of RNAi was first noted in Caenorhabditis elegans as a novel mechanism of post-transcriptional gene silencing, and thereafter it was confirmed in many eukaryotes. mRNA of a targeted gene is cleaved by an RNA-induced silencing complex (RISC), a complex of sequence-specific double-stranded RNA molecules called siRNA and a nuclease. Each siRNA targeted against ataxia telangiectasia-mutated protein kinase (ATM), ATM- and Rad3-related protein kinase (ATR) or DNA-dependent protein kinase catalytic subunit (DNA-PKcs), which contributes to DNA repair machinery, suppresses the gene expression of their respective genes, leading to enhanced radiosensitivity or chemosensitivity. Interestingly, this strategy using siRNAs can be applied for hyperthermic cancer therapy as well as radiation cancer therapy, because we recently obtained data showing that siRNA targeted for a DNA repair protein enhances heat sensitivity. In this review, we mentioned possible effectiveness of siRNA as a sensitizer in hyperthermic cancer therapy.

1. Signal transduction for apoptosis after heating

1-1. p53 pathway

In cancer therapy, the biological implications of radiation-induced apoptosis have recently been focused. We have shown that mutant (mp53) and deletion-type cancer cells of tumor suppressor gene p53 were more resistant to radiation than the wild-type p53 (wtp53) cancer cells using human cultured squamous cell carcinoma cell lines (SAS cells bearing wtp53) and p53-null human lung cancer cell lines (H1299 cells) which were transfected with mp53 or wtp53 gene. DNA array analysis has shown that the expression of apoptosis-inductive genes, such as DNA fragmentation factor-40 (DFF40), caspase-3, -8, -9, -10 and caspase and RIP adapter with death domain (CRADD), was increased by X-ray irradiation in SAS/neo, but not in SAS/mp53. The p53-dependent radiation sensitivity of SAS cells was considered to be induced by the expression of these apoptosis-related genes. The p53-dependent radiation sensitivity was also shown in in vivo experiments using nude mice transplanted with SAS/mp53 or SAS/neo cells. In clinical investigations in human cervical carcinomas, p53-dependent apoptosis-related factors such as bcl-2 associated x (Bax) and B-cell lymphoma/leukemia-2 (Bcl-2) have been reported to be good candidates for predictive indicators for radio-cancer therapy; that is, the survival rate of cancer patients with positive response of Bax and negative response of Bcl-2 is higher than that of cancer patients with negative response of Bax and positive response of Bcl-2.

In contrast, our understanding of the physiological functions of heat-induced p53-dependent signal transduction in human cancer cells is still vague as compared with that of radiation-induced p53-dependent signal transduction. We have reported the p53-dependent heat sensitivity of human cancer cell lines. SAS/mp53 cells and mp53-transfected human glioblastoma cells (A-172/mp53 cells) had a lower survival rate or incidence of apoptosis via Bax than neo control cells. DNA array analysis has shown that an anti-apoptosis-related gene, IL-12, expresses more intensely in SAS/mp53 cells than SAS/neo cells. These results strongly suggest that the heat sensitivity of cancer cells depends on...
the p53 status. Furthermore, we have confirmed p53-dependent heat sensitivity by in vivo experiments \(^{21}\). The rate of tumor growth in response to heat treatment was slower in wtp53 tumor-transplanted mice than in mp53 tumor-transplanted mice. In accordance with this, the incidence of apoptosis via caspase-3 was higher in wtp53 tumor than in mp53 tumor. We have reported p53-dependent hyperthermic enhancement of tumor growth inhibition in X-ray or carbon-ion beam-irradiated mice as well \(^{22}\).

Heat-induced p53-dependent signal transduction pathways are shown in Fig. 1. ATM phosphorylated by heat activates p53 \(^{23}^{24}\) and the p53 induces Bax-mediated apoptosis via caspase-3 \(^3\), like p53 activated by genotoxic stress \(^{25}^{26}\). This p53-dependent signal transduction is one of the pathways for heat-induced apoptosis. In another p53-mediated pathway, FS-7-associated-surface antigen (Fas), a downstream factor of p53, also activates the caspase family \(^{27}^{28}\). The signal transduction pathway via Fas is also likely to contribute to heat-induced p53-dependent apoptosis in human lymphoid cells \(^{29}\) and human colorectal carcinoma cells \(^{30}\). The survival rate of the colorectal carcinoma cells was well correlated with apoptosis induction \(^{30}\).

Fig. 1. Heat-induced signal transduction pathways for apoptosis and cellular proliferation, and inhibitors of signaling factors. DC; dicoumarol; GM, geldanamycin; KN, KNK437 (N-formyl-3, 4-methylene-dioxo-y-butyrolactam); LY, LY 294002 (2-(4-morpholino)-8-phenyl-4H-1-benzopyran-4-one); PD, PD98059 (2-(2’-amino-3’-methoxyphenyl)-oxanaphthalene-4-one); RC, radicicol; SB, SB203580 (4(4-fluorophenyl)-2-(4-methylsulfanyl-phenyl)-5-(4-pyridyl)1H-imidazole); SS, staurosporine; UC, UCN-01 (7-hydroxystaurosporine); WM, wortmannin. Full-names of other abbreviations are shown in the text.
1-2. JNK pathway

JNK, which is one of three major mitogen-activated protein kinases (JNK, ERK and p38), is activated by heat in vitro \( ^{31} \) and in vivo \( ^{32} \) \( ^{33} \) and the activated JNK induces apoptosis of cells \( ^{4} \) \( ^{5} \) through a phosphorylation cascade that is distinct from the ERK or p38 mediated-cascade \( ^{34} \) (Fig. 1). In heat-induced activation of JNK, ceramide acts as an important second messenger. Hydrolysis of sphingomyelin by sphingomyelinase (SMase) in response to heat causes an increase of the cellular content of ceramide \( ^{35} \). Besides ceramide-dependent JNK-mediated apoptosis \( ^{36} \) \( ^{38} \), ceramide-independent JNK-mediated apoptosis in response to heat was reported in fibrosarcoma cells \( ^{39} \). JNK activates downstream caspase-dependent \( ^{4} \) \( ^{5} \) and caspase-independent signaling pathways for heat-induced apoptosis \( ^{40} \). These reports imply that there may be multiple pathways for JNK-mediated heat-induced apoptosis. Interestingly, it has been reported that ceramide enhances heat-induced apoptosis by suppressing anti-apoptotic HSP72 through post-transcriptional regulation \( ^{41} \). HSP72 suppresses heat-induced apoptosis by accelerating the inactivation of JNK \( ^{42} \) \( ^{43} \).

It was reported that JNK was not activated by heat in the spleen and lung tissues of mice but was activated in cultured organs or fibroblasts derived from the spleens or lungs of mice \( ^{44} \). The activity and amount of JNK protein were most abundant in the brain among the tissues examined. Heat-induced JNK activation occurred in heart, liver and kidney, but not in lung, brain or spleen. These in vivo experiments demonstrated that the pattern of heat-induced JNK activation is very different from in vitro experiments. Unknown physiological factors in animals may affect the mechanisms controlling JNK activation. Accordingly, hyperthermic effects on the activation of JNK may be organ specific. In the rat liver, in vivo heat shock causes activation of JNK, but does not trigger the cleavage of poly (ADP-ribose) polymerase, which is an accompanying cellular response of apoptosis \( ^{45} \). A clinical report on chemotherapy \( ^{45} \) showed that JNK was activated in ovarian carcinoma from patients treated with platinum agents and paclitaxel. The level of JNK activity was correlated with the survival of patients. The report \( ^{46} \) showed a significant role of JNK activity in the clinical course of ovarian cancer. Improved prognosis may thus be associated with a high level of JNK activity.

2. Signal transduction for anti-apoptosis after heating and inhibitors of this process

2-1. Akt-mediated pathway

A serine/threonine kinase, Akt, is known to mediate many biological actions affecting anti-apoptotic/cell survival responses \( ^{47} \) \( ^{49} \). Amplification of the Akt gene is frequently observed in various types of cancer cells. The activity of Akt is high in cancer cells defective in phosphatase and tensin homologue deleted on chromosome 10 (PTEN), which downregulates Akt activity. These abnormalities of Akt have been considered to be closely related to tumorigenesis. Thus, Akt is now becoming a promising and attractive molecular target for enhancing apoptosis \( ^{50} \) and cancer therapy \( ^{51} \).

Akt is activated by various types of stress, including heat, through phosphorylation. The heat-induced Akt-centered anti-apoptosis signal transduction pathway is shown in Fig. 1. Akt is activated by heat through phosphatidylinositol-3-kinase (PI3-K) and the 3-phosphoinositide-dependent kinase-1 (PDK1)-mediated phosphorylation pathway \( ^{52} \). The activity of Akt is maintained by HSP90 which protects Akt against dephosphorylation via protein phosphatase 2A (PP2A) \( ^{53} \). Activated Akt interferes
Enhancement of heat sensitivity by signal transduction inhibitors • K. Ohnishi et al.

with the heat-induced apoptosis pathway by phosphorylating caspase-9 [54] and Bcl2-antagonist of cell death protein (Bad) [55] [56]. Akt also blocks the translocation of orphan nuclear receptor HMR (Nur77) and Forkhead family proteins into the nucleus, resulting in the upregulation of Fas ligand and TNFRI-associated death domain (TRADD) protein expression as a result of phosphorylation of these transcription factors [54] [55]. Furthermore, Akt phosphorylates nuclear factor \( \kappa \)B (NF-\( \kappa \)B). The phosphorylated NF-\( \kappa \)B facilitates the synthesis of proteins involved in cell survival [56]. Heat-induced Akt activation is also observed in vivo [57]. PI3-K activity increases after hyperthermia in the liver of rat via a tyrosine kinase-dependent mechanism [45]. Glycogen synthase kinase-3 (GSK-3), which is a possible downstream factor of PI3-K through Akt, undergoes hyperphosphorylation. Thus, in vivo heat-induced activation of the Akt pathway plays an important role in the protection against apoptosis [45]. Akt plays a central role in multiple pathways for the inhibition of heat-induced apoptosis, and thus one expects that interference with the Akt pathway by inhibitors would enhance heat-induced apoptosis.

2. Inhibitors of Akt pathway

2.1. PI3-K inhibitors

Wortmannin inhibits the activity of DNA-PK at lower doses and ATM at higher doses (Fig. 1). As DNA-PK and ATM contribute to the DNA repair machinery, it has been reported that wortmannin enhances the radiosensitivity of cancer cells [58] [59]. Another report showed that wortmannin enhances the radiosensitivity of ataxia telangiectasia cells, but it does not enhance the radiosensitivity of DNA-PK-deficient cells [60]. Therefore, it is possible that wortmannin sensitizes cells to radiation through inhibition of the DNA-PK-mediated DNA repair. Enhancement of apoptosis by wortmannin has also been reported in a human breast cancer cell line [61]. In contrast to wortmannin, 2-(4-morpholinyl)-8-phenyl-4H-1-benzopyran-4-one (LY294002) sensitizes not only radiosensitivity but also heat-sensitivity (our unpublished data). The mechanism of the inhibition of heat-induced PI3-K activation seems to be different between wortmannin and LY294002. LY294002 might sensitize cells to heat via the inhibition of unknown heat-induced anti-apoptotic pathway. Radio-sensitization with LY294002 has been reported by in vitro [58] and in vivo [62] experiments but heat sensitization with LY294002 has not been reported.

2.2. PDK1 inhibitor

7-hydroxystaurosporine (UCN-01) has been used as a PDK1-inhibitory drug in clinical trials. UCN-01 induces Akt inactivation by inhibiting PDK1 directly (Fig. 1), resulting in the suppression of the survival signals and the induction of apoptosis [63]. Staurosporine has also been reported to suppress PDK1 directly [63].

2.3. NF-\( \kappa \)B inhibitor

Dicoumarol, a coumarin derivative, was reported to potentiate TNF-induced apoptosis in HeLa cells, probably by blocking the anti-apoptotic effect of NF-\( \kappa \)B and is currently used clinically [64]. Since NF-\( \kappa \)B is a target of Akt, dicoumarol is a potential hyperthermic cancer therapeutic inhibitor of NF-\( \kappa \)B.

2.4. HSP inhibitors

HSP27, 72 and 90 play inhibitory roles in varied signal transduction pathways for apoptosis (Fig. 1).
One of these roles is to interfere with the formation of the apoptosome, which consists of apoptosis protease-activating factor-1 (Apaf-1), caspase-9 and cytochrome c. HSP27, 72 and 90 interfere with apoptosome formation in different manners and consequently suppress the activation of caspase-3. HSP27 binds to cytochrome c released from the mitochondrion and blocks the binding of cytochrome c to Apaf-1. Another anti-apoptotic function of HSP27 is to regulate the activity of Akt. HSP72 and HSP90 bind to Apaf-1 and depress the activation of caspase-9. In addition, HSP72 suppresses heat-induced apoptosis by inactivating JNK or by antagonizing apoptosis-inducing factor (AIF). HSP90 is a molecular chaperone whose association is required for the stability and function of signaling proteins that promote the growth and/or survival of cancer cells. Client proteins associated with HSP90 include Akt, breakpoint cluster region (Bcr)-Ableson tyrosine kinase 1 (Abl), Raf-1, ErbB1/epidermal growth factor receptor (EGFR), ErbB2/Her2, mutated p53 and hypoxia-inducible factor 1α (HIF-1α).

HSP90 inhibitors such as geldanamycin and radicicol are attractive anti-cancer agents. Geldanamycin and radicicol indirectly down-regulate the activity of Akt through interfering with the association between HSP90 and PDK1. After the dissociation of PDK1 with HSP90, the PDK1 is proteasome-dependently degraded and the degradation of PDK1 results in elimination of the binding of PDK1 to Akt. The kinase domain of PDK1 is essential for complex formation with HSP90, and the inhibitors interact with this domain. Geldanamycin and radicicol also alter the complex formed between HSP90 and Raf-1. This leads to a decrease in the Raf-1 level and consequently to disruption of the Raf-1-Map kinase-ERK kinase (MEK)-MAPK signaling pathway.

17-allylamino-17-demethoxygeldanamycin (17-AAG) is a geldanamycin analog that is currently being used in Phase I clinical trials in the USA and UK. 17-AAG also affects the Akt-mediated signal transduction pathway involved in tumor cell proliferation and survival. Early results from phase I trials have demonstrated that 17-AAG has an inhibitory function similar to that of geldanamycin but shows a significantly improved toxicity profile.

A coumarin antibiotic, Novobiocin, interacts with an ATP-binding domain in the carboxyl terminus of HSP90 and suppresses the chaperone function of HSP90. Novobiocin is already being used in cancer therapy.

A newly synthesized chemical, N-formyl-3,4-methylenedioxy-y-butyrolactam (KNK437) suppresses the induction of HSPs at the mRNA level. Since KNK437 does not affect the constitutive amounts of HSPs, the inhibitory mechanism of this compound seems to be due to inhibition of the activation of heat shock factor 1 (HSF1) or the binding of HSF1 to heat shock element (HSE). Based on this manner of inhibition, KNK437 is regarded as a potentially useful agent to suppress the heat tolerance of cancer cells which is frequently observed as a negative effect of fractionated hyperthermic cancer therapy.

3. Signal transduction for cellular proliferation after heating and inhibitors of this process

3-1. Mitogen-activated protein kinase (MAPK) cascade

The mitogen-activated protein kinase (MAPK) pathway is a key signal transduction cascade that links diverse extracellular stimuli to proliferation, differentiation, and survival. Heat activates the MAPK cascade (ceramide to Ras/Raf/MEK/ERKs) called the classical MAPK cascade (Fig.1).
This cascade induces activation of intracellular substrates including transcription factors, such as Ets-like protein 1 (Elk-1), c-Jun, and activating transcription factor 2 (ATF2), and other protein kinases. Inhibition of the activity of ERK1 by overexpression of a dominant-negative ERK1 enhanced the heat sensitivity of cells. In contrast, cells stably overexpressing the wild-type ERK1 developed resistance to killing by heat. Ceramide activates Raf-1 via metabolism to sphingomyelin after heat shock. The activation of MAPKs by heat is cell type-specific, because myeloid leukemic cells such as HL-60, U937 and K562 cells have no ability to activate Raf-1, while NIH3T3 fibroblasts do possess such ability. The activation of the MAPKs cascade is lacking in some types of cancer cells. MAP kinase kinases (termed MEK1 and MEK2) involved in downstream signaling of Raf-1 activate ERK1/2 by phosphorylation of both threonine and tyrosine residues. Heat shock induces ERK1/2 activation in rat brain. Inhibition of the MAPKs cascade, in which a key target kinase is MEK, is expected to provide sensitization of cancer cells to hyperthermic cancer therapy.

3-2. Stress-activated MAPK, p38

p38, called stress-activated MAPK, has been characterized based on its activation in response to extracellular stress stimuli, including heat stress in vitro and in vivo. As shown in Fig.1, p38 is involved in a phosphorylation cascade (ceramide to MAP kinase-ERK kinase kinases (MEKKs) / apoptosis signal-regulating kinases1 (ASK1) / MAP kinase kinases (MKKs) / p38) that is distinct from the above-described Ras/Raf/MEK/ERKs cascade, and it is involved in the regulation of cellular proliferation, differentiation and transformation. In vivo experimental results have shown that MKK3 and/or MKK6 are activated downstream to MEKKs in response to hyperthermia in rats. These reports taken together suggest that selective inhibition of p38 is also useful for sensitization to heat sensitivity. However, there are some reports showing that activation of p38 seems to be involved in the induction of apoptosis in some cell types upon various stress stimuli. This discrepancy in the functions of p38 may result from the different genetic backgrounds among cancer cells.

3-3. Inhibitors of MAPK pathway

2-(2'-amino-3'-methoxypheny1)-oxanaphthalen-4-one (PD98059) is an inhibitor that selectively depresses the activity of MEK (Fig.1). Inhibition of MEK by PD98059 prevents subsequent phosphorylation of ERK substrates that contribute to cell growth and survival. PD98059 abrogates the clonogenicity of leukemic cells but has minimal effects on normal hematopoietic progenitors. The suppressive function of PD98059 has been reported to be effective in transplanted tissue or solid tumors. PD98059 enhances paclitaxel-induced apoptosis in solid tumor cell lines. 4-(4-fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)1H-imidazole (SB203580) suppresses p38 activation selectively and consequently interferes with signaling induced by transforming growth factor-β (TGF-β). Inhibition of p38 by SB203580 induces enhanced heat sensitivity of lung cancer cells (our unpublished data) and suppresses invasion of cancers in which p38 is activated. In contrast to the positive function of SB203580, a negative function by which SB203580 leads cells to become resistant to cisplatin has been reported. RWJ-67657 and FR167653 are also inhibitors of p38.
4. DNA repair pathway and siRNAs targeted against repair gene

Double-strand breaks (DSBs) of DNA are induced by radiation and cause severe damage in irradiated cells. As shown in Fig. 2, there are two main pathways by which such breaks can be repaired, homologous recombination (HR) and non-homologous end joining (NHEJ). DNA repair proteins protect mammalian cells from potentially lethal and/or tumorigenic lesions resulting from DNA damage. Possible DNA damage induced by heat has been previously reported. Our recent study has shown that DNA repair proteins are likely to respond to heat in a similar manner as to radiation (unpublished data). Taken together, HR and NHEJ may also play an important role in cell survival in response to heat.

HR repair is highly conserved from bacteria to humans. HR has been considered to be the primary mechanism of DSB repair in yeast but not in mammals. The homologous region of a sister chromatid serves as a template for reconstruction of the damaged site by DNA synthesis. Thus, HR repair functions in cells at the S and G2 phases of the cell cycle, while NHEJ occurs throughout the cell cycle. The repair mechanism involving HR in mammalian cells is now receiving attention. Recent reports have revealed that H2AX around damaged sites of DNA is phosphorylated by ATM in response to radiation,
and then the Nijimegen breakage syndrome 1 (NBS1)/meiotic recombination 11 (MRE11) /Rad50 complex assembles into foci at the sites of γH2AX (Fig. 2). Phosphorylation of NBS1 by ATM helps MRE11/Rad50 to approach γH2AX 114). NBS1 is homologous to yeast Xrs2, which forms a complex with MRE11 and Rad50. Other repair proteins, such as Rad51, Rad52, Red54, breast cancer susceptibility protein1 (BRCA1) and BRCA2, are required for the subsequent execution step of DNA repairing.

NHEJ repair appears to be a dominant pathway for DSB repair in vertebrates, because DSB repair-defective mutants analyzed to date have been defective in NHEJ 115). DNA-dependent protein kinase (DNA-PK) 116), the X-ray repair cross-complementing 4 (XRCC4) gene product 117), DNA ligase IV 118-120), NBS1/MRE11/Rad50 and Sir2, 3, 4 121) are necessary for the NHEJ pathway (Fig. 2). DNA-PK consists of DNA-PKcs and Ku, which is a heterodimer of 70 and 80 kDa subunits (Ku70 and Ku80, respectively) 122-124). Cells defective in either Ku70 or Ku80 are sensitive to radiation 125) 126).

RNAi has been applied for radiation or chemical sensitization in normal human fibroblasts 8) or human cancer cells 9). Those reports revealed that sensitivity to radiation/anti-cancer agents is higher in cells transfected with siRNA targeted against DNA-PKcs or ATM/ATR than in cells transfected with control vector. We have observed that DNA-PKcs-targeted siRNA sensitizes human lung cancer cells to radiation p53-independently. Furthermore, we have found that siRNA-targeted against one of HR repair genes sensitizes cells to heat. These results provide strong evidence for the potential use of siRNA targeted against HR and NHEJ repair genes as a novel hyperthermia sensitizer.

5. Perspectives on hyperthermic cancer therapy combined with inhibitors

We propose here prospective inhibitors for sensitizing cancer cells to hyperthermia. These inhibitors may be applied for advanced hyperthermic cancer therapy, but a significant obstacle exists for the development of selective targeted inhibition. Many interactive networks of signaling pathways probably regulate cell proliferation and survival. It is possible that other signaling pathways will become dominant in cell proliferation when a key signaling pathway is blocked by an inhibitor. Furthermore, since many cancer cells forming a tumor are heterogeneously exposed to different cellular conditions (low pH, hypoxia and low nutrition), different survival signaling pathways are activated in a tumor. Therefore, inhibition of a target specific for an inhibitor may not alter the malignant phenotype of a tumor. However, HSP90 inhibitors such as geldanamycin and 17-AAG may overcome this problem, because they lead to the depletion of multiple oncogenic client proteins involved in different signaling pathways for cellular proliferation. It is very important for hyperthermic cancer therapy to identify signaling factors relating to survival of cancer cells and use appropriate inhibitors against the signaling factors.

Acknowledgment

This work was supported by Grants-in-Aid from the Ministry of Education, Science, Sports, Technology and Culture of Japan.

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Enhancement of heat sensitivity by signal transduction inhibitors • K. Ohnishi et al.


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温熱で誘導されるシグナル伝達因子を標的とした癌温熱治療

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要 旨：癌温熱治療において治療効果の増進をめざした増感剤や small interference RNAs (siRNAs) に関する研究はいまだ少ない。温熱で誘導されるシグナル伝達経路を標的とした化学物質や siRNAs の基礎研究が強く望まれている。ここではアポトーシス、抗アポトーシス/細胞増殖あるいは DNA 修復に関与するシグナル伝達因子を特異的に阻害する薬剤と siRNAs の分子機序についてまとめた。我々は本総説であげた温熱増感剤が癌温熱治療において高い治療効果をもたらすことを期待してい