

The Stress Kinase p38 α as a Target for Cancer Therapy

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Abstract

p38 α is a ubiquitous protein kinase strongly activated by stress signals, inflammatory cytokines, and many other stimuli, which has been implicated in the modulation of multiple cellular processes. There is good evidence in the literature that p38 α plays an important tumor-suppressor role by interfering with malignant cell transformation. This is mainly based on the ability of the p38 α pathway to regulate tissue homeostasis by integrating signals that balance cell proliferation and differentiation or induce apoptosis. However, recent reports have also illustrated

protumorigenic functions for p38 α . Thus, p38 α signaling may facilitate the survival and proliferation of tumor cells contributing to the progression of some tumor types. In addition, p38 α activation helps tumor cells to survive chemotherapeutic treatments. In all these cases, the inhibition of p38 α has a potential therapeutic interest. Further elucidation of the context-dependent functions of p38 α signaling in tumoral processes is of obvious importance for the use of inhibitors of this pathway in cancer therapy. *Cancer Res*; 75(19); 3997–4002. ©2015 AACR.

Introduction

The p38 mitogen-activated protein kinase (MAPK) signaling pathway plays important roles in the ability of cells to integrate external stimuli and elaborate appropriate responses. This pathway plays a key role in the stress response, but inflammatory cytokines and many different non-stress stimuli can also activate p38 MAPK signaling, leading to the regulation of numerous cellular processes.

Four p38 MAPK family members have been identified: p38 α , p38 β , p38 γ , and p38 δ . p38 α is ubiquitously expressed usually at high levels, whereas p38 β is expressed at lower levels. The expression patterns of p38 γ and p38 δ are more restricted. Most of the functions that are generally ascribed to p38 MAPKs actually refer to p38 α , which is encoded by the *MAPK14* gene. More than 100 proteins can be directly phosphorylated by p38 α and a significant proportion of them is involved in the regulation of gene expression (1, 2). In addition, the p38 α pathway can control at different levels the production of extracellular signaling molecules, such as cytokines, chemokines, and growth factors (3).

Deregulation of protein kinase signaling underlies many human pathologies. Cancer is a complex disease that arises through a multistep, mutagenic process, which inevitably involves changes in the wiring of signaling pathways that are normally tightly regulated to maintain tissue homeostasis. The mutations sometimes affect protein kinases directly involved in promoting cancer cell growth. However, tumor development also involves interactions of the tumor cells with the surrounding

microenvironment that not only contributes to primary tumor growth, for example by promoting neovascularization, but may facilitate dissemination of tumor cells as well as the metastatic process at large. These interactions involve secreted signaling molecules such as transforming growth factor β (TGF β) and interleukin-6 (3). Thus, different steps of tumorigenesis involve substantial changes in the signaling pathways of several cell types.

Initial studies addressing the function of p38 α were mainly based on the use of small-molecule chemical inhibitors. More recently, the use of RNAi technologies, the generation of mice with genetic inactivation of specific p38 MAPK family members, and the development of more potent and specific chemical inhibitors have allowed a better characterization of the contribution of p38 α to particular cellular processes. Here, we will focus on p38 α signaling in tumor cells and will review data indicating that p38 α may either facilitate or interfere with tumor development, depending on the context.

Tumor Formation

The p38 α signaling pathway has been classically considered a tumor suppressor, mainly based on its ability to negatively regulate proliferation and induce differentiation of several cell types. Despite the relevance of p38 α signaling in tumor suppression, inactivating mutations of p38 α have not been consistently identified in human tumors. This probably reflects that cancer cells can benefit from the versatility of this signaling pathway to control multiple cellular processes. In line with this idea, recent reports have provided evidence for a dual role of p38 α in several cancer types (Fig. 1).

Breast

There is evidence that p38 MAPK suppresses breast tumor initiation. For example, Wip1-knockout mice show reduced breast tumorigenesis upon expression of oncogenes, which correlates with higher p38 MAPK phosphorylation, and the p38 MAPK inhibitor SB203580 abolishes the effect of Wip1 deficiency in tumorigenesis (4). However, treatment with the p38 MAPK

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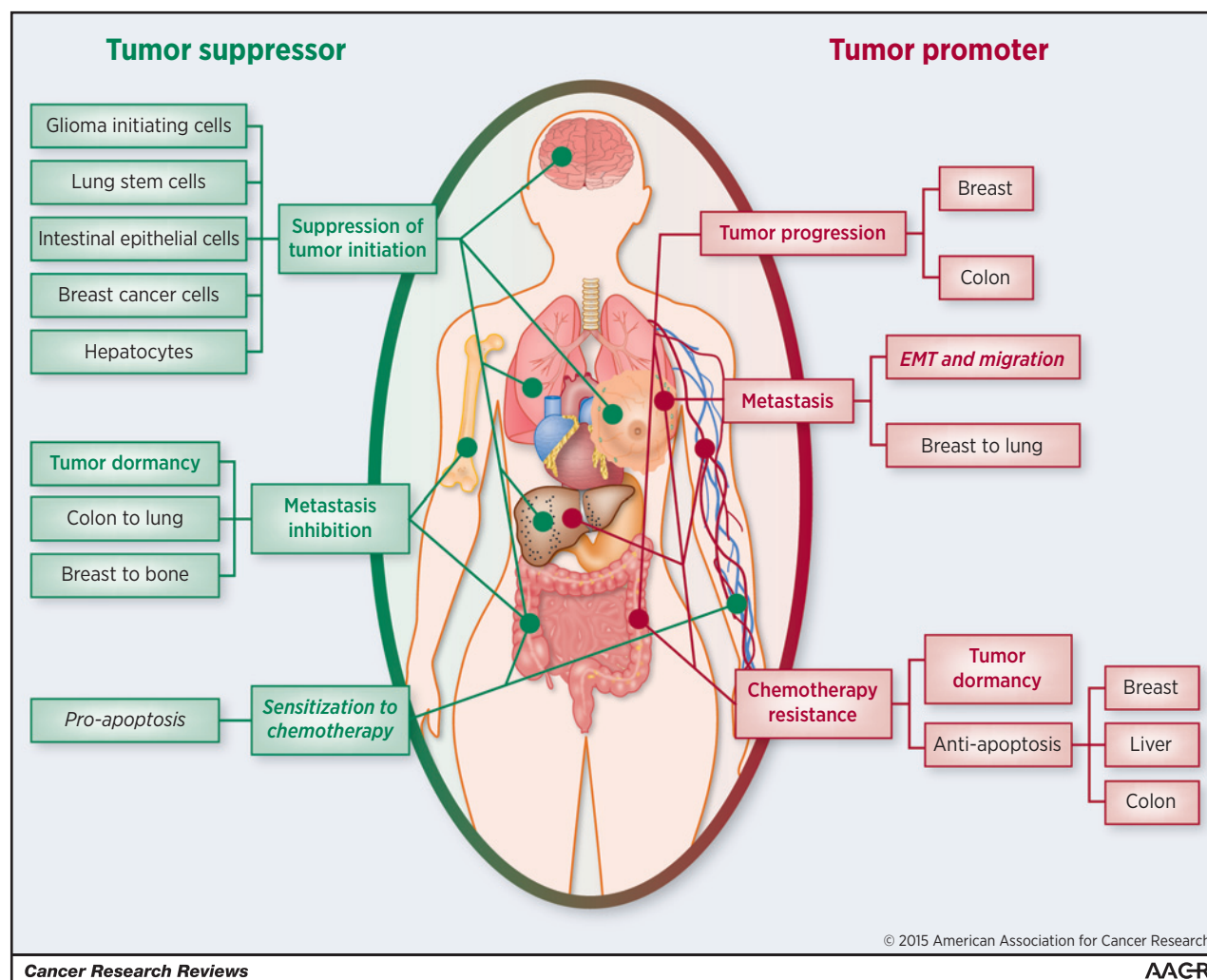


Figure 1.

In vivo roles of p38 α in tumorigenesis based on mouse models. As a tumor suppressor (green), an important function of p38 α is to regulate tissue homeostasis by balancing cell proliferation, differentiation, and apoptosis. But p38 α can also function as a tumor promoter (red), facilitating tumor cell survival and dissemination. The tissues where *in vivo* studies were performed are indicated. Italics, extensive *in vitro* studies but no evidence of *in vivo* relevance.

inhibitor LY2228820 reduces tumor growth in xenografts of human breast cancer cell lines (5), and the p38 MAPK inhibitor PH797804 impairs the growth of breast tumors induced by polyoma middle T (PyMT) expression in mice (6). Moreover, high levels of active p38 MAPK have been correlated with poor prognosis, lymph node metastasis, and tamoxifen resistance in breast cancer patients (3), supporting a role for p38 α in breast tumor progression.

Colon

p38 α regulates intestinal homeostasis and the integrity of the colon epithelia. Downregulation of p38 α in intestinal epithelial cells increases proliferation, reduces the number of mucus-producing goblet cells and affects epithelial barrier function by altering tight junction assembly (7, 8). As a consequence, mice with p38 α -deficient intestinal epithelial cells are more susceptible to colitis-associated colon tumorigenesis (7). In contrast, downregulation of p38 α in colon tumor cells or pharmacologic inhibition using PH797804 reduces tumor burden in mice (7). Treatment with the p38 MAPK inhibitor SB202190 also reduces

colon tumor growth either in xenografts of human colon cancer cell lines or in mice that express APC^{min} (9). These results support that p38 α facilitates colon tumor progression.

Lung

p38 α controls self-renewal of the lung stem and progenitor cells by inhibiting proliferation and facilitating differentiation. Inactivation of p38 α leads to a hyperproliferative and immature lung epithelium that is sensitized to K-Ras^{G12V}-induced tumorigenesis (10). However, increased p38 MAPK phosphorylation has been reported in human lung tumors compared with normal tissue (3), suggesting that this pathway might contribute to lung tumor progression.

Liver

p38 α controls liver homeostasis by negatively regulating the proliferation of hepatocytes. Deletion of p38 α in mouse hepatocytes facilitates the N-nitrosodiethylamine (DEN)-induced hepatocellular carcinoma through enhanced reactive oxygen species (ROS), activation of the JNK/c-Jun pathway, and increased

proliferation (11, 12). In addition, high ROS levels induce hepatocyte death and the release of IL1 α , which promotes compensatory proliferation and DEN-induced liver cancer (12). In both studies, p38 α was deleted before the induction of hepatocellular carcinoma, suggesting a suppressor role in tumor initiation. Whether p38 α could function as a tumor promoter at later stages of liver tumorigenesis has not been investigated.

Other tissues

p38 α balances proliferative and growth-inhibitory signals during normal hematopoiesis (13), and overactivation of p38 α induces hematopoietic stem cell apoptosis, resulting in the development of certain myelodysplastic syndromes (14). In the same line, the p38 α pathway has been proposed to negatively regulate stemness of glioma-initiating cells, by inducing loss of self-renewal and promoting differentiation (15). Moreover, p38 α is required for the survival of pancreas cancer cell lines and high-grade human pancreas tumors show enhanced levels of phosphorylated p38 MAPK, which correlate with reduced expression of the phosphatase DUSP1 (16).

Taken together, the available data suggest an explanation for the dual role of p38 α in tumorigenesis. During oncogene-induced tumor initiation and in the early response to carcinogens, p38 α mainly acts as a tumor suppressor by maintaining cell homeostasis and eventually inducing cell death, for example in response to the accumulation of high ROS levels. However, p38 α function is sometimes altered in the tumor cell so that it favors tumor progression. This might be due to changes in gene expression programs that accompany malignant cell transformation or could be driven by different stimuli available in the microenvironment. It should be noted that other signaling proteins are known to have dual functions in tumorigenesis. For example, TGF β family members potently inhibit cell growth and induce apoptosis in normal cells, suppressing the early stages of tumorigenesis. However, as the tumor progresses, genetic and/or biochemical changes allow TGF β to stimulate tumor progression by acting on both cancer cells and stromal cells of the tumors (17).

Metastasis

The dissemination of the primary tumor to distant body sites is a major determinant of cancer patient mortality. Downregulation of p38 α signaling has been associated with the ability of human colon cancer cells to form lung metastases from established liver metastases in orthotopic mouse models. This is mediated by increased expression of parathyroid hormone-like hormone (PTHrH), a cytokine that induces endothelial cell death in the lung facilitating extravasation of the tumor cells. Consistent with these results, low levels of p38 MAPK phosphorylation in human colorectal tumors inversely associate with higher relapse probability in patients (18). Another study has linked the p38 MAPK pathway with inhibition of breast cancer metastasis to bone by acting downstream of Kringle 1 domain of hepatocyte growth factor (HGFK1) and leading to decreased expression of the receptor activator of nuclear factor- κ B (RANK; ref. 19).

On the other hand, p38 α can positively regulate the migration of several cell types, including tumor cells, as well as the processes of epithelial-to-mesenchymal transition (EMT), tumor cell intravasation, and colonization of distant sites (20). A recent report has implicated p38 α , downstream of the ubiquitin-conjugating enzyme Ubc13 and the kinase TAK1, in the metastatic dissemi-

nation of breast cancer cells to the lung in mouse models. Moreover, p38 α and Ubc13 expression correlates with worse overall survival in human patients with breast cancer (21).

The molecular basis for the pro- or antimetastatic roles of p38 α is not clear. To elucidate the different behaviors observed, it would be important to address how cells interpret p38 MAPK signals, considering both the nature and extent of the p38 α pathway activation and the cellular context in which it occurs.

Dormancy

Disseminated cells from the primary tumor that reach a metastatic site can sometimes enter a dormancy state, which is regulated by signals from the local microenvironment. Studies in head and neck carcinoma models have shown that the switch from tumor cell proliferation to dormancy is regulated by the balance between the extracellular signal-regulated kinase (ERK)-1/2 and p38 MAPK pathways (22). Growing metastatic lesions show sustained ERK1/2 activity and reduced p38 MAPK activity, and genetic or pharmacologic inhibition of p38 MAPK suffices to interrupt dormancy and restore tumor growth *in vivo*. Results in prostate and breast cancer cells support the idea that a low ERK1/2-p38 MAPK signaling ratio induces dormancy (22).

The microenvironment signals that regulate tumor cell dormancy are starting to be elucidated. For example, high levels of TGF β 2 expressed in bone marrow result in a "restrictive" microenvironment that favors dormancy of head and neck squamous carcinoma cells, whereas more "permissive" microenvironments like lung express lower TGF β 2 levels, resulting in short-lived dormancy and metastatic growth. Interestingly, TGF β 2 probably regulates dormancy through p38 MAPK signaling as high TGF β 2 in bone marrow reduces the ERK1/2-p38 MAPK ratio by activating p38 MAPK (23).

Tumor dormancy can be considered as a double-edge sword, as it interferes with the formation of macro-metastasis but may help tumor cells to resist chemotherapy treatments. Considering dormancy as a survival mechanism implies that tumor cells achieve sufficient p38 MAPK activity levels to induce growth arrest without triggering apoptosis, so that subsequent regrowth is possible. It will be important to confirm that tumor dormancy mechanisms identified in experimental models operate in cancer patients.

Chemotherapy

Activation of p38 α has been proposed to mediate the antitumoral effects of some chemotherapeutic drugs. In colon cancer cell lines, p38 α is necessary for the apoptosis induced by cisplatin and fluorouracil, which are accounted for by the p38 α -mediated phosphorylation of p53 (24, 25). Apoptosis induced by rituximab in chronic lymphocytic leukemia cells and by STI-571 (imatinib) in the chronic myeloid leukemia cell line K562 (24) are also mediated by p38 α . Moreover, pharmacologic inhibition of p38 α reverses the growth-inhibitory effects of STI-571 on primary leukemic granulocyte/macrophage progenitors from patients with CML (26). These studies have been mostly performed with cell lines and more *in vivo* studies are needed to validate the extent to which p38 α mediates chemotherapy effects.

On the other hand, there is strong *in vitro* and *in vivo* evidence supporting that p38 α inhibitors potentiate the effect of chemotherapeutic drugs. Thus, the response to cisplatin is enhanced by p38 α inhibition, resulting in ROS-dependent upregulation of the JNK pathway in colon and breast cancer cells (6). Pharmacologic

inhibition of p38 α in mouse models cooperates with cisplatin to reduce the size and malignancy of breast tumors induced by PyMT (6) or subcutaneous tumors formed by xenografted human colon cancer cell lines (27). Similarly, p38 α inhibitors sensitize colon cancer cell lines to the treatment with fluorouracil or irinotecan (28) and cooperate with arsenic trioxide to induce differentiation and apoptosis of leukemia cells *in vitro* and *in vivo* (29). A recent study has shown that p38 α inhibition, either mediated by shRNAs or by pharmacologic compounds, sensitizes mouse hepatocellular carcinomas to sorafenib therapy (30). Therefore, the combination of sorafenib and p38 MAPK inhibition looks promising to overcome therapy resistance in human hepatocellular carcinoma. In some cases, high levels of p38 MAPK activity in chemoresistant cancer cells have been correlated with the upregulation of P-glycoprotein, a plasma membrane transporter involved in the efflux of chemotherapeutic drugs like cisplatin or doxorubicin (27).

The survival of cancer cells upon nutrient withdrawal has been proposed to rely on the reorganization of the glucose metabolism by p38 α (31). Thus, starvation induces higher glucose uptake through HIF1 α stabilization and proteasome-dependent degradation of PFKFB3, leading to autophagy activation, which is reversed by the downregulation or inhibition of p38 α . The modulation of autophagy could underlie the protective effect of p38 α on starvation-induced cell death. In general, p38 α appears to orchestrate adaptive responses to unfavorable stress conditions, which could contribute to the emergence of tumor-resistant phenotypes, making this pathway a potential therapeutic target for the enhancement of conventional therapies. An additional mechanism by which p38 α could facilitate chemotherapy resistance is by inducing tumor cell dormancy, as nondividing cells are thought to be more resistant to cytotoxic treatments.

In summary, increasing evidence supports an important role of p38 α facilitating tumor chemoresistance. The *in vivo* studies are critical, given that extracellular factors present in the tumor microenvironment could influence the response of tumor cells to particular treatments. Reports using cancer cell lines *in vitro*, although useful, do not reflect the complex interactions between different cell types in the tumor microenvironment, which may sometimes result in misleading information.

Therapeutic Opportunities

The ability of p38 α to suppress the initial phases of malignant cell transformation is supported by genetic evidence in mouse models of lung and liver cancer (10, 11). Intriguingly, the proapoptotic function of p38 α is sometimes impaired in tumor cells and there is evidence supporting that p38 α can facilitate colorectal tumor maintenance in mouse models (7). Thus, p38 α inhibitors may suffice to impair the growth of tumors where this pathway is required for cancer cell proliferation or survival, but these inhibitors could potentially stimulate tumorigenesis in other tissues. There is also evidence for dual roles of p38 α in metastasis, as downregulation of p38 α signaling facilitates the metastatic spread of colon cancer cells from liver to lung (18), whereas a p38 α pharmacologic inhibitor attenuates breast cancer metastasis (21). The development of new therapeutic strategies clearly requires a better understanding of the specific targets involved in the different functions of p38 α and how they contribute to specific tumoral processes.

In addition, recent data strongly implicate p38 α signaling in the resistance to chemotherapeutic treatments. A number of drugs

used for cancer chemotherapy induce damage DNA, resulting in cell death, and p38 α activation has been shown to mediate cell survival in response to DNA damage. In these cases, p38 α inhibition sensitizes tumor cells to the chemotherapeutic response and enhances cell death, implying that this pathway may facilitate drug resistance. This prosurvival effect of p38 α can be probably explained by several mechanisms, including the contribution of this pathway to the repair of the damaged DNA prior to the cell entering mitosis. Intriguingly, experiments with cell lines suggest that p38 α activation might occasionally have the opposite result mediating drug-induced cell death, so the inhibitors would interfere with antitumoral effects. It should be noted that the specific signaling pathways activated by DNA damage might vary depending on the cell type, the DNA damage stimuli, and the extent of DNA damage. Moreover, some p38 α targets are tissue specific, such as the phosphorylation of GSK3 β at Ser³⁹⁹ that is thought to occur predominantly in brain (32). This could explain why sometimes p38 α inhibition results in chemotherapy sensitization while in other cases it is linked to resistance.

The combination of p38 α inhibitors with chemotherapeutic drugs looks like a promising strategy for the treatment of some tumors, as in the case of cisplatin and irinotecan for breast and colon cancer (6, 28) and sorafenib for hepatocellular carcinoma (30). However, it is difficult to forecast at the moment what type of tumors would benefit from the combined therapies. Predictive biomarkers would be very useful to select the patients who are most likely to benefit from the p38 α inhibitors. These could be based on the elucidation of the p38 α pathway activation status in different tumor types, for example by immunohistochemistry analysis with phospho-specific antibodies against p38 α or selected downstream targets such as ATF2 (30), or by using p38 α pathway-specific gene expression signatures. Results obtained from genetically modified mice have also provided interesting insights into how patients could be selected for therapies based on p38 α inhibitors. For example, disruption of the p38 α and p38 β genes results in mouse embryo malformations (33), suggesting that these inhibitors should not be used to treat pregnant woman. Likewise, genetic downregulation of p38 α sensitized to K-Ras^{G12V} induced lung tumorigenesis (10), suggesting that inhibitors of this pathway should not be considered in populations at risk of lung cancer such as heavy smokers. Interestingly, the p38 MAPK inhibitor losmapimod has given promising results in a clinical trial for myocardial infarction (34), suggesting that p38 MAPK inhibitors could be potentially useful in patients with both cardiac diseases and cancer.

A large number of p38 α inhibitors, which generally also inhibit p38 β , have been developed. Currently, there are about 50 ongoing clinical studies using p38 MAPK inhibitors from different pharmaceutical companies for a wide variety of diseases (<https://clinicaltrials.gov/>). Potential lack of efficacy could be due to the p38 α pathway playing a less important role in a particular function than originally anticipated. Alternatively, cells could bypass the p38 α inhibition by engaging other p38 MAPK family members, which could have overlapping functions with p38 α . It remains to be established the extent to which different p38 MAPK family members might interplay during tumor development. Pleiotropic interactions with other signaling pathways may also allow cells to bypass p38 α inhibition, as it is not unusual that several pathways are simultaneously activated and contribute to a particular cellular process. Given the redundancy in signaling pathways and the

adaptive capacity of cancer cells, drug combinations are increasingly being investigated for therapy.

An alternative therapeutic approach could be to target other components in the p38 α pathway. Identification and characterization of the substrates involved in the different p38 α -regulated processes could provide a larger repertoire of potential targets to reduce the deleterious effects while maintaining protective functions. This strategy might alleviate the possibility of toxicities due to p38 α homeostatic functions and could also improve selectivity. For example, the MAPK-activated protein kinase-2 (MK2) regulates posttranscriptional expression of cytokines and other processes downstream of p38 α signaling. MK2-null mice are healthy and do not have any overt phenotype, suggesting that targeting MK2 could be less toxic than p38 α inhibition. Interestingly, downregulation of MK2 has been reported to sensitize p53-deficient lung tumor cells to apoptosis induced by cisplatin and doxorubicin in mouse models (35).

The inhibition of protumorigenic roles of p38 α while maintaining its growth-inhibitory and apoptosis-inducing effects would be also an interesting therapeutic approach. Development of these ideas requires a much better definition of the molecular mechanisms that underlie these events. Generation of reagents that specifically activate or inhibit the p38 α pathway in particular cells types could be also very useful.

Conclusions

p38 α is a broadly expressed protein kinase that is very abundant in most cell types and can be activated by stress and many other extracellular signals, participating in the regulation of mul-

tiples cellular processes. The available data indicate that the p38 α pathway can regulate tumorigenesis at different levels and through distinct mechanisms depending on the cell type and the tumoral stage (Fig. 1). Of particular interest, is the evidence indicating that p38 α often facilitates tumor cell survival in response to chemotherapeutic treatments. It would be very interesting to elucidate biomarkers for tumor-promoting activities of p38 α , so that tumor types and chemotherapeutic drugs that could benefit from p38 α inhibition are identified. Of note, therapy outcomes would be affected by the functions of p38 α signaling in different cell types of the tumor microenvironment, which are likely to impinge on tumor development. Further studies are clearly needed to realize the full potential of p38 α inhibitors in cancer therapy, but we believe that recent results are encouraging. The devil is in the detail.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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