Thursday, 23 October 2008 08:00–09:45

PLENARY SESSION 4

Targeting autophagic pathways

239 INVITED

Oncogenes and tumor suppressor genes control autophagy

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Multiple oncogenes (in particular phosphatidylinositol 3-kinase, PI3K; activated Akt1; anti-apoptotic proteins from the Bcl-2 family) inhibit autophagy. Similarly, several tumor suppressor proteins (such as BH3-only proteins; death associated protein kinase-1, DAPK1; the phosphatase that antagonizes PI3K, PTEN; tuberous sclerosic complex 1 and 2, TSC1, TSC2; as well as LKB1/STK11) induce autophagy, meaning that their loss reduces autophagy. Beclin-1, which is required for autophagy induction acts as a haploinsufficient tumor suppressor protein, and other essential autophagy mediators (such as Atg4c, UVRAG and Bif-1) are bona fide oncosuppressors. One of the central tumor suppressor proteins, p53 exerts an ambiguous function in the regulation of autophagy. Within the nucleus, p53 can act as an autophagy-inducing transcription factor. Within the cytoplasm, p53 exerts a tonic autophagy-inhibitory function, and its degradation is actually required for the induction of autophagy. The role of autophagy in oncogenesis and anti-cancer therapy is contradictory. Chronic suppression of autophagy may stimulate oncogenesis. However, once a tumor is formed, autophagy inhibition may be a therapeutic goal for radiosensitization and chemosensitization. Altogether, the current state-of-the art suggests a complex relationship between cancer and deregulated autophagy that must be disentangled by further in-depth investigation.

240 INVITED

Role of autophagy in cancer resistance

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Drug resistance is a major obstacle that limits the effectiveness of cancer therapy. Therefore, we need to explore new strategies that overcome the emerging problem of drug resistance. Autophagy, an evolutionarily conserved response to stress, has recently been implicated in cancer initiation and progression. Accumulating evidence indicates that numerous cancer treatments cause autophagy, which is recognized as one of the resistance mechanisms against cancer treatment. In contrast, autophagy has also been thought to induce cell death by various cancer therapies, which is designated as type-2 programmed cell death or autophagic cell death. In tumor cells, the role of autophagy may depend on types of tumors or stimuli, stages of tumorigenesis, or extent of insult. Thus, it is essential to determine the role of autophagy in tumor cells in order to increase efficacy of the treatment by manipulating autophagic process. Today we present that a new alkylating agent temozolomide (TMZ) and γ-irradiation (IR), which are representative treatments for malignant glioma but not very effective, induce autophagy in vitro and in vivo settings and that inhibition of autophagy pharmacologically or genetically results in sensitization of tumor cells to TMZ and IR. Our data suggest that, when autophagy is cancer resistant mechanism, agents that disrupt autophagy are a promising new strategy to enhance the efficacy of cancer therapies in drug resistance.

241 INVITED

Novel therapeutic targets within the autophagic pathway

W.N. Hait. *USA*

Abstract not received

242 INVITED

Targeting apoptosis-resistant cancer cells through autophagic cell death

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Background: Lung cancer remains the leading cause of cancer death worldwide. Radioresistance of lung cancer cells results in unacceptable rate of loco-regional failure. Although radiation is known to induce apoptosis, our recent study showed that knockdown of pro-apoptotic proteins Bak and Bax resulted in an increase in autophagic cell death and lung cancer radiosensitivity in vitro. To further explore the potential of apoptosis inhibition as a way to sensitize lung cancer for therapy, we tested M867, a novel chemical and reversible caspase-3 inhibitor, in combination with ionizing radiation in vivo and in vitro.
Methods and Findings: M867 reduced clonogenic survival in H460 lung cancer cells (DER = 1.27, p = 0.007) compared to the vehicle-treated treated cells. We found that administration of M867 with ionizing radiation in an in vivo mouse hind limb lung cancer model was well tolerated, and produced a significant tumor growth delay compared to radiation alone. A dramatic decrease in tumor vasculature was observed with M867 and radiation using von Willebrand factor staining. In addition, Ki67 index showed >5-fold reduction of tumor proliferation in the combination therapy group, despite the reduced levels of apoptosis observed with terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling staining. Radiosensitizing effect of M867 through inhibiting caspases was validated using caspase-3/-7 double-knockout (DKO) mouse embryonic fibroblasts (MEF) cell model. Consistent with our previous study, autophagy contributed to the mechanism of increased cell death, following inhibition of apoptosis. In addition, matrigel assay showed a decrease in in vitro endothelial tubule formation during the M867/radiation combination treatment.
Conclusions: M867 enhances the cytotoxic effects of radiation on lung cancer and its vasculature both in vitro and in vivo. M867 has the potential to prolong tumor growth delay by inhibiting tumor proliferation. Clinical trials are needed to determine the potential of this combination therapy in patients with locally advanced lung cancer.

Thursday, 23 October 2008 10:15–12:00

PLENARY SESSION 5

Molecular targets – state of the science C

243 INVITED

Aurora kinase inhibitors: more than one opportunity?

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Aurora serine/threonine kinases are a family of three proteins, which play key roles in critical phases in mitosis in controlling chromosome assembly and segregation. Inhibition of Aurora A (AA) function results in cell cycle arrest and monopolar mitotic spindles formation. Inhibition of Aurora B (AB) results in a premature exit from mitosis due to abolishment of a critical spindle checkpoint and in endoreduplication. Aurora C (AC) has been less studied. The interest for Aurora kinases inhibition as an anticancer strategy arose from the hope to target mitosis more specifically and from the over expression of Aurora kinases in most human cancers where AA gene is frequently amplified. Ectopic over expression of AA was shown to induce oncogenic transformation, while ablation resulted in cell death in tumor cells but in reversible cell cycle arrest in normal cell. Interestingly, AA over expression was shown to induce resistance to some chemotherapeutic agents through different mechanisms. Although an oncogenic activity of AB was not demonstrated, elevated AB activity is known to promote Ras-mediated transformation by enhancing oncogenic signaling and by inducing aneuploidy. It was also observed that patients with AB-positive carcinoma had a poor prognosis compared to those with AB negative tumors. The link of AC and cancer is less well defined.
Initially a few companies started to work on small molecule Aurora inhibitors and the first 2 phase I clinical studies have been initiated in solid tumors in June 2004 by Nerviano Medical Sciences with PHA-739358. To date more than 20 programs are on going in various companies, and more than 10 compounds have reached the stage of clinical trials. These compounds are selective Aurora kinase A or B inhibitors, or pan-Aurora kinase inhibitors. Most compounds show some cross-reactivity with other cancer-relevant kinases including Abl (wt and T315I), Ret, TrkA, FGFRs, VEGFRs, JAK2, or FLT3.
In solid tumors dose limiting toxicities were essentially neutropenic infection and febrile neutropenia. Some specific compounds were put on hold due to CNS events, prolongation of QTc, or pulmonary issues. Safety profiles consist mainly of grade (G) 3–4 neutropenia, G1–2 fatigue, anorexia, and nausea. G1–2 diarrhea in up to 50% of patients is mainly seen in the case of oral inhibitors. Reduction of histone H3 phosphorylation has been described as a pharmacodynamic biomarker of AB inhibition in human tissues. Clinically relevant stable diseases have been described in most publications in various tumors. Preliminary clinical efficacy starts to be reported in various tumor types: partial responses in ovarian cancers in single agent trials at recommended phases II doses, and in small cell lung cancer with G-CSF support. Better characteristics of patients who might benefit from Aurora inhibition have still to be elucidated.