kinase activity and decreased the activity of S6 kinase, suggesting an involvement of mTOR pathway in the eEF-2 kinase regulation of autophagy. These results suggest that: (1) eEF-2 kinase plays a regulatory role in the autophagic process in tumor cells; (2) eEF-2 kinase is a downstream member of the mTOR signaling; (3) eEF-2 kinase may promote cancer cell survival under conditions of nutrient deprivation through regulating autophagy. Therefore, eEF-2 kinase may be a part of a survival mechanism in glioblastoma, and targeting this kinase may represent a novel approach to cancer treatment.

Supportive care agents

221 POSTER

Leteprinim attenuates cisplatin-induced neuropathy

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Sensory peripheral neuropathy is a dose-limiting toxicity of cisplatin chemotherapy. Cisplatin-induced neuropathy is generally associated with a reduction in the signal amplitude and velocity of sensory nerve, reflecting nerve fiber dysfunction. This dysfunction can be revealed in a rat model by behavioral sensory test such as hot plate test and by electrophysiological measures.
The aim of our study was to determine whether leteprinim (SPI-205) could improve changes and dysfunctions associated with cisplatin-induced neuropathy. In the present study, the neuroprotective effect of different formulations of SPI-205 was evaluated in a rat model of cisplatin-induced neuropathy.
Ten week-old female Dark Agouti rats were randomly distributed in 5 experimental groups: (a) a control group (n = 17), receiving sc treatment with the Placebo of SPI-205 suspension; (b) a control group (n = 17), receiving sc treatment with the Placebo of SPI-205 salt (0.9% NaCl); (c) a cisplatin-intoxicated group (n = 17), (d) a cisplatin-intoxicated group (n = 17) receiving sc treatment with SPI-205 suspension (50 mg/kg/d); (e) a cisplatin-intoxicated group (n = 17) receiving sc treatment with SPI-205 soluble salt solution (50 mg/kg/d). Cisplatin was given iv at 2 mg/kg biweekly during 4 weeks; SPI 205 was given at 50 mg/kg daily for 7 weeks. Body weight and survival rate were recorded daily. Animals were evaluated functionally by hot plate and EMG testing once a week for 7 weeks. Sciatic nerves were harvested from 5 animals per group at week 5 for histological analysis.
Results showed that treatment with SPI-205 markedly attenuates cisplatin-induced nerve dysfunction and accelerates the recovery from this disorder. These improvements were evident in most of studied parameters (H-wave amplitude and latency, SNCV and axonal degeneration) and seemed to be in good correlation with the improvement observed in the hot plate test. The results were similar with the two SPI-205 formulation
Histological results showed that the axonal diameter of cisplatin group is slightly increased. This might represent axonal degeneration, a phenomenon observed as a consequence of cisplatin intoxication in developing rat brain (Rzeski et al, 2004). SPI-205 treatment seemed to completely prevent this axonal swelling.
In summary, the present study showed that daily treatment with 50 mg/kg SPI-205 injected subcutaneously can improve cisplatin-related sensory neuropathy in rats.

Toxicology methods and models

222 POSTER

Study of in vitro tumor invasion and metastasis: the application of an innovative three dimensional tumor model

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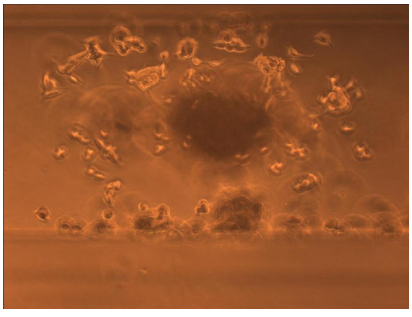
Background: As the biological characteristics of malignant tumors, invasion and metastasis are the most dangerous situations during the process of tumor growth and progression. About 60% of cancer patients are detected with metastasis at the time of first diagnosis, and 80% of them actually die from tumor invasion and metastasis. Since it is difficult to observe the process of cancer invasion and metastasis in a patient, and the spontaneous tumor in animal models rarely metastasizes in a short term, there is a pressing need to develop an in vitro three dimensional (3D) tumor model with the features that mimic the characteristics of in vivo solid tumor for the study of tumor invasion and metastasis.
Materials and Methods: Several tumor cell lines such as liver/colon/ovary/lung/breast/stomach cancer, and insulinoma were obtained from ATCC. These cells were seeded and cultured in an invented 3Dtissue culture device. Then the in vitro invasion and metastasis of the tumor were observed after the "primary" tumors were reestablished from these cell lines in this culture device.
Results: The biological characteristics of tumor invasion and metastasis were observed. For example, the rapid growth of tumor cells, the stationary and translocative motility, cellular structure of microvillus, lamellipodia and pilipodia, spread and adhesion of the tumor cells, the penetrative invasion, the dislodge and/or moving away of the tumor cells from the parent tumor, etc. For liver and lung cancers, many tumor cells were actively spread and moved to the surrounding and distant areas. These cells adhered and demonstrated a colonial dominance growth pattern and formed multiple metastasis tumors in the distant areas. The onset time, the frequency and the degree of tumor invasion and metastasis were different among different types of tumors. Two different types of liver cancers behaved quite differently in the biological characteristics of tumor invasion and metastasis. The process of tumor invasion and metastasis could be dynamically followed up for several months without destroying the specimens.



Conclusions: To our best knowledge, this is the first report of direct investigation of tumor invasion and metastasis in vitro after the 3D tumor models are rebuilt from tumor cell lines. Our results indicate that this innovative 3D tumor model can be used as an extremely valuable tool for the in vitro study of tumor invasion and metastasis, for the selection of subpopulations of the tumor cell with different potential of invasion and metastasis, and for the evaluation of potential tumor invasion and metastasis in individual cancer patient for the selection of proper treatment and the prediction of prognosis. Apply this 3D tumor models as an in vitro assay for the molecular targeted medicine study may help the discovery of therapeutic strategy specifically designed for the prevention and treatment of tumor invasion and metastasis.

223 POSTER

An innovative three dimensional tumor model for in vitro study of tumor biology

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Background: Malignant tumors in patients have different biological characteristics based on their intrinsic genetic diversity and the development of heterogeneous sub-clones with divergent phenotypes. Identifying the tumor malignancy behavior such as the proliferative ability and metastatic potential in vitro is critical to choice the appropriate treatment regimens and to evaluation the prognosis. Here we report an in vitro investigation of tumor biology by using an innovative three dimensional (3D) tumor model.
Materials and Methods: Various types of tumor cell lines such as liver, colon, ovary, lung, breast, stomach cancer and insulinoma were obtained from ATCC. These tumor cell lines were seeded and cultured in an innovative three dimensional tissue culture device. We observed the biological characteristics of each tumor such as the tumor morphology, the proliferative ability, in vitro invasion and metastasis, and apoptosis. For the comparison, normal stomach cells, hepatocytes and pancreas islet cells were cultured under same condition as control.
Results: The tumors rebuilt in vitro demonstrated the characteristics associated with solid tumor in vivo. Such as unlimited rapid growth of the cells and structurally arranged containing a necrotic core surrounded by an outer shell of proliferating viable cells.
Different types of tumors exhibited their unique morphology. For example, a round global shape for small cell type lung cancer; irregular nodular and cauliflower shapes for colon cancer. Some of the tumors expressed tumor associated antigen. For example, liver cancer expressed AFP, colon cancer secreted CEA and ovary cancer was associated with CA-125.
The biological characteristics of tumor invasion and metastasis were also observed: the stationary and translocative motility, cellular structure of microvillus, lamellipodia and pilipodia, spread and adhesion of the tumor cells, the penetrative invasion, dislodge and/or moving away of the tumor