Tumorigenesis

Major finding: Running suppresses tumor growth in mouse tumor models by increasing natural killer cell infiltration.

Mechanism: Running induces plasma IL6 and epinephrine, which mobilize IL6-sensitive natural killer cells.

Impact: Exercise may enhance natural killer cell–mediated antitumor immune responses.

EXERCISE REDUCES TUMOR INITIATION AND PROGRESSION IN MOUSE MODELS

Epidemiologic studies have suggested that regular exercise protects against cancer development and recurrence, but the mechanisms by which regular exercise may protect against cancer remain unknown. Pedersen and colleagues investigated the effects of wheel running on tumor incidence and progression in multiple mouse tumor models. In one example, four weeks of wheel running prior to subcutaneous melanoma cell implantation markedly reduced tumor growth compared to non-running control mice and inhibited lung metastasis when cells were intravenously injected. Running also significantly reduced tumor incidence in chemically induced liver tumors, decreased tumor volume in a lung carcinoma model, and delayed the onset of spontaneous melanoma in transgenic mice. Microarray analysis of subcutaneous melanomas revealed that running upregulated a number of immunologic and inflammatory pathway genes. Moreover, tumors from running mice exhibited elevated infiltration by natural killer (NK) cells, and depletion of NK cells abrogated the antitumor effects of running. Mechanistically, running was associated with increased serum levels of epinephrine (EPI), which was required for the running-induced reduction in tumor volume. Plasma levels of IL6 also increased during exercise, and EPI reduced the fraction of IL6Rα-positive splenic NK cells, suggesting that IL6-sensitive NK cells were mobilized to tumor sites. Consistent with these findings, anti-IL6 antibodies prevented the exercise-induced reduction in tumor growth and reduced tumor infiltration by NK cells. Taken together, these data indicate that exercise can reduce tumor initiation and progression via an EPI-dependent mobilization of IL6-sensitive NK cells, and suggest a potential mechanism whereby exercise may enhance NK cell antitumor activity in multiple cancer types. ■

Pedersen L, Idorn M, Olofsson GH, Lauenborg B, Nookaew I, Hansen RH, et al. Voluntary running suppresses tumor growth through epinephrine- and IL-6-dependent NK cell mobilization and redistribution. Cell Metab 2016;23:554–62.

Clinical Trials

Major finding: Aurora A kinase inhibition combined with chemotherapy is tolerable in neuroblastoma.

Clinical relevance: Patients with advanced neuroblastoma respond to alisertib plus cytotoxic chemotherapy.

Impact: Aurora A kinase inhibition may be combined with irinotecan and temozolomide to treat neuroblastoma.

ALISERTIB COMBINED WITH CHEMOTHERAPY ACHIEVES RESPONSE IN NEUROBLASTOMA

Chemotherapy with irinotecan and temozolomide is used as a salvage therapy in patients with relapsed or refractory neuroblastoma. The combination has only modest response rates, but is well tolerated, providing the possibility of combining it with new therapies. In preclinical studies, the Aurora A kinase inhibitor alisertib was cytotoxic to neuroblastoma cells, and early clinical studies of alisertib in adult patients have shown it may be combined with chemotherapy. In a phase I dose escalation study, DuBois and colleagues determined the maximum tolerated dose of alisertib with fixed doses of irinotecan and temozolomide in 22 patients with relapsed or refractory neuroblastoma. After the first course of treatment, two patients developed dose-limiting toxicities including neutropenia, and two patients had grade 3 diarrhea, prompting amendment of the protocol to add myeloid growth factor support and cephalosporin diarrhea prophylaxis. The maximum tolerated dose for alisertib was determined to be 60mg/m^2. The majority of patients exhibited hematologic toxicities, including thromboycytopenia (84%) and neutropenia (69%). Diarrhea and nausea were the most common nonhematologic toxicities. Pharmacokinetic profiles indicated that there were no interactions between alisertib and irinotecan. Across all dose levels, the overall response rate was 31.8%, including a complete response rate of 22.7%, and the progression-free survival rate at two years was 52.4%. None of the five patients who had previously received irinotecan responded, whereas among the irinotecan-naïve patients the response rate was 41.2%. In addition, the response rate was poorer in patients with *MYCN*-amplified tumors (16.7%) compared to patients with *MYCN*-nonamplified tumors (35.7%). Overall, the results of this phase I trial demonstrate that alisertib can be combined with irinotecan and temozolomide, and this combination has a promising response rate and progression-free survival rate in patients with relapsed and refractory neuroblastoma. These findings support further investigation of alisertib with irinotecan and temozolomide in larger clinical trials. ■

DuBois SG, Marachelian A, Fox E, Kudgus RA, Reid JM, Groshen S , et al. Phase I study of the Aurora A kinase inhibitor alisertib in combination with irinotecan and temozolomide for patients with relapsed or refractory neuroblastoma: A NANT (new approaches to neuroblastoma therapy) trial. J Clin Oncol 2016 Feb 16 [Epub ahead of print].