Tumor Heterogeneity

Major finding: Variation in the growth dynamics of genetically stable clones modulates chemotherapy responses.

Approach: The genetic and functional diversity of single colorectal cancer clones was assessed in mice.

Impact: Nongenetic factors also generate clonal heterogeneity and contribute to therapeutic tolerance.

FUNCTIONAL VARIABILITY DRIVES COLORECTAL CANCER HETEROGENEITY

Accumulation of genetic mutations in cancer gives rise to subclones with diverse growth and metastatic potentials. In addition, nongenetic factors, such as interactions with the tumor microenvironment and epigenetic changes, are thought to generate heterogeneity among genetically similar subclones, but it is not clear whether this results in functional differences in tumor propagation among individual cancer cells. To investigate this question *in vivo*, Kreso and colleagues tracked the fates of 150 GFP-labeled, single-cell–derived clonal lineages isolated from 10 primary human colorectal cancers through serially transplanted xenografts in mice. Copy number alteration profiling and sequencing of mutational hotspots demonstrated that xenografts remained genetically stable throughout serial transplantation and retained the genomic characteristics of the corresponding primary tumor. However, the clones exhibited significant functional variability in their repopulation and growth dynamics in multiple patient samples and could be classified into 5 types based on distinct patterns of emergence and longevity in sequential transplants: persistent, short-term, transient, and fluctuating clones, as well as resting clones that were initially dormant but initiated proliferation in later transplants. Mutational analysis confirmed the absence of genetic variability between different clone types isolated from the same tumor, suggesting that cells within a single genetic clone are functionally diverse. Intriguingly, these heterogeneous clone types also exhibited variable responses to chemotherapy, as treatment with oxaliplatin selectively decreased the proportion of persistent clones but promoted the dominant outgrowth of previously dormant, resting clones in secondary regrown tumors. This effect was independent of acquired genetic mutations in response to chemotherapy, underscoring the importance of nongenetic mechanisms in generating intratumoral heterogeneity. These results demonstrate that inherent functional diversity modulates colorectal cancer growth and therapeutic sensitivity and suggests that dormancy may be an adaptive mechanism used by tumors to facilitate tumor reinitiation after chemotherapy. ■

Kreso A, O'Brien CA, van Galen P, Gan O, Notta F, Brown AM, et al. Variable clonal repopulation dynamics influence chemotherapy response in colorectal cancer. Science 2012 Dec 13 [Epub ahead of print].

Clinical Trials

Major finding: Selumetinib is well tolerated and active in recurrent LGSC of the ovary or peritoneum.

Concept: LGSC of the ovary exhibits MAPK activation and a high frequency of *KRAS* and *BRAF* mutations.

Impact: Further clinical studies of MAPK pathway inhibitors are warranted for patients with LGSC.

SELUMETINIB HAS ACTIVITY IN LOW-GRADE SEROUS OVARIAN CANCER

Low-grade serous carcinomas (LGSC) of the ovary and peritoneum are histologically and molecularly distinct from high-grade serous carcinomas and largely resistant to cytotoxic chemotherapeutics. Because LGSCs frequently harbor activating mutations in components of the MAPK pathway, including the *KRAS* and *BRAF* oncogenes, Farley and colleagues assessed the safety and efficacy of selumetinib, a selective small-molecule inhibitor of MAP/ERK kinase (MEK) 1 and MEK2, in patients with LGSC. In an open-label, single-arm phase II trial, 52 women with pathologically confirmed, recurrent LGSC of the ovary or peritoneum were treated with selumetinib, and the proportion of patients with an objective tumor response was determined as the primary endpoint. Although 58% of the patients had previously received several chemotherapeutic treatments, 8 patients (15%) experienced an objective response, including 1 complete response and 7 partial responses, and 65% had stable disease after selumetinib treatment. The median progression-free survival (PFS) was 11 months, with a PFS longer than 6 months in 63% of patients, and median overall survival was not yet reached. Selumetinib was well tolerated, as grade 4 toxicities only occurred in 6% of patients; the most common grade 3 toxicities were manageable with dose reductions and included gastrointestinal, dermatologic, and metabolic adverse events. Intriguingly, genomic analysis of tumor DNA samples indicated that objective response to selumetinib was not significantly associated with the presence of a mutation in *KRAS* or *BRAF*. These findings suggest MEK1/2 inhibition as a more effective and less toxic strategy for the treatment of patients with recurrent LGSC compared with cytotoxic chemotherapy and support additional investigation of agents targeting the MAPK pathway in this disease. ■

Farley J, Brady WE, Vathipadiekal V, Lankes HA, Coleman R, Morgan MA, et al. Selumetinib in women with recurrent low-grade serous carcinoma of the ovary or peritoneum: an open-label, single-arm, phase 2 study. Lancet Oncol 2012 Dec 21 [Epub ahead of print].