



Caring for Carcinoid Foundation
Investigator's report for 2006: Ramesh A. Shivdasani, MD, PhD

In 2006 our research on carcinoid tumor biology was divided over 3 areas and focused on 2 of these three. First, we completed a high-resolution analysis of chromosomal copy number alterations (CNAs) in human carcinoid tumor samples that we had started the previous year. We evaluated 24 primary and metastatic small intestine carcinoid tumors derived from 18 patients. Many studies that use the same single-nucleotide polymorphism (SNP) technique rely on a single method and do not confirm the data independently; as a result, investigators question the significance of some of the published literature on other tumor types. Wishing to avoid similar concerns for our analysis of bowel carcinoid tumors, we verified most of the salient findings using independent methods. In some other tumors, small areas of the genome reveal CNAs that point to individual genes as candidates for a role in disease causation. In contrast, we found that the most common anomalies in intestinal carcinoid tumors consisted of gains or losses of whole chromosomes or larger regions; entire loss of chromosome 18 was the most common finding, appearing in 13 of the 24 samples. Moreover, the magnitude of chromosomal gains was modest in comparison to those reported in other cancers. Unfortunately, the studies have thus far failed to identify a single common or group of genetic abnormalities in carcinoid tumors that directly suggest new avenues for therapy. However, our study resulted in the interesting and unexpected observation that intestinal carcinoid tumors fall into two distinct classes: those with many chromosomal changes and those with very few. We believe these two groups reflect alternative paths of tumorigenesis and we will attempt in the future to better understand the basis for these differences.

Second, an important goal in carcinoid tumor biology is to identify the cell of its origin, a goal that the Foundation's scientific advisory board independently regarded as a priority at the scientific summit last December. Investigators agree that genetic experiments in mice may provide the most satisfying answers to this question. Our laboratory has exploited its expertise in the study of gastrointestinal development to address fundamental questions about the origin and diversity of endocrine cells in the gut. We engineered a strain of mice lacking in a single new gene we identified in the laboratory, one that produces a transcription factor, i.e., a protein that regulates the activity of many other genes. This strain of mice has a virtual absence of selected stomach endocrine cells, close relatives of the presumptive target of intestinal carcinoid tumors, and implicates our novel transcription factor in the genesis of stomach endocrine cells. Such studies outline the molecular networks that control individual cell types and help dissect cellular hierarchies in tissues. We will continue our investigation of this and similar modified mouse strains to define discrete endocrine cell lineages in the adult gastrointestinal tract.

Finally, we moved closer to our goal of isolating intestinal progenitor cells as a step toward studying how these cells make the choice between proliferation and rest. The experiments are particularly challenging because the progenitor cells in question require replication of their normal intestinal environment in the culture dish. We have been isolating the cells from adult mouse intestine required to provide the support for progenitor cell culture and using various technical manipulations to mimic the natural niche for their growth in the laboratory. Success in these endeavors would represent a significant research advance and enable powerful analysis of the cells that give rise to carcinoid tumors. As tumor samples yield information about specific

gene mutations in carcinoid tumors, it is these kinds of experimental models that will need to be exploited to make full use of the genetic information and design rational, targeted therapies.

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