Achilles’ (Other) Heel: Non-Oncogene Addiction in Multiple Myeloma

Oncogene addiction has been regarded as the Achilles’ heel of cancer, based on the idea that silencing an oncogene’s expression will prove lethal in certain cancers. However, new research suggests that multiple myeloma—a cancer of antibody-producing plasma cells—may have a fatal vulnerability that is better described as a “non-oncogene addiction.”

There is no curative treatment for the many subtypes of multiple myeloma, each of which utilizes distinct oncogenic pathways. Thus, developing therapeutic alternatives not based on type-specific oncogenes is very attractive to clinicians and researchers. Recent research highlighting the role of the protein IRF4 in the survival of myeloma cells suggests that this protein may provide a therapeutic target for all myeloma subtypes.

In the July 2008 issue of Nature, a team of NCI and NIH researchers, led by Staff Scientist Arthur Shaffer III, Ph.D., and Deputy Chief Louis Staudt, M.D., Ph.D., of CCR’s Metabolism Department, reported results of a study utilizing small hairpin RNAs (shRNAs) to identify potential drug targets for multiple myeloma. The team observed that silencing the gene IRF4 killed 10 different cell line models representing many subtypes of myeloma. Importantly, most of these myeloma models lacked any genetic abnormality in IRF4 but were nevertheless completely dependent upon IRF4 for survival, a phenomenon that the investigators characterized as “non-oncogene addiction.”

In normal lymphocytes, IRF4 is a transcription factor helping to initiate responses to foreign antigens and to generate plasma cells. To understand the molecular basis for IRF4 addiction in multiple myeloma, the investigators characterized the repertoire of genes that are activated by IRF4 in myeloma cells. They found that IRF4 turns on genes in myeloma cells that are also induced during normal lymphocyte activation but are silenced in healthy plasma cells, from which myeloma is derived. Thus, IRF4 controls an aberrant regulatory network in multiple myeloma.

Staudt, Shaffer, and their collaborators found a peculiar relationship between IRF4 and the oncogene MYC, which has a prominent role in myeloma pathogenesis. In their experiments, silencing IRF4 suppressed MYC expression and, conversely, silencing MYC suppressed IRF4 expression. Their observations suggest a model in which IRF4 and MYC reinforce the expression of each other in a cycle that perpetuates cancer cell proliferation and survival.

The findings suggest that blocking IRF4 expression may be an attractive and broadly applicable therapeutic option for the many subtypes of multiple myeloma. More generally, the phenomenon of non-oncogene addiction promises to provide a new range of therapeutic targets in cancer.

References:

To learn more about Dr Staudt’s research on hematologic malignancies, please see “Making Sense of Lymphoma: The Definition Makes a Difference” in CCR Connections, Vol. 1, No. 2, or visit his CCR Web site at http://ccr.cancer.gov/staff/staff. asp?profileid=5780.

To learn more about Dr Shaffer’s research on the role of non-oncogene addiction in cancer, please visit his Web site at http://ccr.cancer.gov/staff/staff. asp?profileid=5790.