A Criminal Identified: NFκB in Lymphoid Neoplasia

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Inducible transcription factors regulate immediate and long-lived cellular responses necessary for adaptation to environmental plasticity. Such responses are mediated to a large degree through changes in gene expression. One transcription factor that serves as a key responder to changes in the environment is NFκB (nuclear factor-κB). NFκB is an evolutionarily conserved signaling molecule that plays a critical role in many biologic processes. Understanding how the transcriptional potential, activity, and selectivity of NFκB are regulated is therefore a topic of intense investigation in numerous laboratories.

NFκB is a family of transcription factors associated with IκB (inhibitor of NFκB) family of inhibitory proteins predominantly localized in the cytoplasm. The common denominator for NFκB activation is the removal of IκB proteins from the DNA-binding subunits of NFκB. The NF-κB pathway undergoes a very tight, although complex, regulatory mechanism in which NF-κB controls its inhibitor IκB transcription and stabilizes IκB proteins. NFκB signaling plays a pivotal role in several cellular and developmental processes, and deregulation of this pathway is suspected in and also causally linked to the initiation and progression of many human pathologies, including those of hematologic origin, *Helicobacter pylori*-associated carcinogenesis, and cancers of the breast, colon, liver, and cervix. NFκB signaling pathway is therefore a target for therapy in malignancies.

At yesterday's Scientific Committee session on Lymphoid Neoplasia, NFκB was in the spotlight in different presentations that summarized the current understanding and progress on this signaling pathway. In the first presentation, Dr. Christina M. Annunziata highlighted the knowledge of how specific modifications, including *p53* tumor suppressor gene, a key regulator of the cell-death cycle, regulate NFκB activity in response to distinct stimuli and how this knowledge will lead to the design of more specific inhibitors of NFκB.

In the third talk, Dr. Peter Leif Bergsagel demonstrated the importance of NFκB in the pathogenesis of multiple myeloma. The author identified, in primary multiple myeloma tumors and in a panel of cell lines, several activating and inactivating mutations that lead to activation of the NF-κB pathway. Interestingly, the level of one of these genes, *TRAF3*, can be used as a surrogate marker to identify patients who appear to be resistant to glucocorticoids and, in contrast, markedly sensitive to proteasome inhibitors.

These data suggest that the NFκB pathway is an important signaling pathway and could be the future cornerstone of targeted therapeutic clinical trials to help improve survival of patients with cancer.