

A Criminal Identified: NF κ B 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 NF κ B (nuclear factor- κ B). NF κ B is an evolutionarily conserved signaling molecule that plays a critical role in many biologic processes. Understanding how the transcriptional potential, activity, and selectivity of NF κ B are regulated is therefore a topic of intense investigation in numerous laboratories.

NF κ B is a family of transcription factors associated with I κ B (inhibitor of NF κ B) family of inhibitory proteins predominantly localized in the cytoplasm. The common denominator for NF κ B activation is the removal of I κ B proteins from the DNA-binding subunits of NF κ B. The NF- κ B pathway undergoes a very tight, although complex, regulatory mechanism in which NF- κ B controls its inhibitor I κ B transcription and stabilizes I κ B proteins. NF κ B 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. NF κ B signaling pathway is therefore a target for therapy in malignancies.

At yesterday's Scientific Committee session on Lymphoid Neoplasia, NF κ B 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 NF κ B activity in response to distinct stimuli and how this knowledge will lead to the design of more specific inhibitors of NF κ B.

In the third talk, Dr. Peter Leif Bergsagel demonstrated the importance of NF κ B 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- κ B 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 NF κ B 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.