Therapeutic Strategies in Lymphoma Based on Oncogenic B Cell Receptor and MYD88 Signaling

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Seeking an unbiased method to discover therapeutic targets in cancer, we developed a loss-of-function genetic screen using genomic-scale libraries of small hairpin RNAs that mediate RNA interference. These "Achilles heel" screens are designed to reveal genes essential for cancer cell proliferation and survival. In a parallel structural genomics approach, we are using RNA-seq to globally identify somatic mutations and other structural abnormalities in cancer. The intersection of these two data sets has helped us to discover novel pathogenetic pathways in the most common type of non-Hodgkin lymphoma, diffuse large B cell lymphoma (DLBCL). The ABC DLBCL subtype has constitutive activation of the NF-kB pathway, which we traced to the signaling adapter CARD11 using the Achilles heel screen. In ~10% of ABC DLBCL tumor biopsies, we discovered recurrent CARD11 mutations that spontaneously activate NF-kB signaling. We also defined a "chronic active" form of B cell receptor (BCR) signaling that activates NF-kB in ABC DLBCLs with wild type CARD11. Such ABC DLBCLs are killed by knockdown of BCR signaling components, such as the kinase BTK, or components of the BCR itself. Over one fifth of ABC DLBCLs have mutations in the CD79B or CD79A subunits of the BCR. In 18% of cases, mutations occur in a single tyrosine residue in the critical "ITAM" signaling motif, generating BCRs that avoid negative autoregulation by the LYN tyrosine kinase. Our Achilles heel screens revealed that ABC DLBCLs depend upon MYD88, a key adapter in Toll receptor signaling. RNA-Seq uncovered somatic mutations in the MYD88 TIR domain in 39% of ABC DLBCLs, with a single point mutation (L265P) accounting for 29% of cases. Genetic evidence suggests an interplay between the BCR and MYD88 signaling pathways in ABC DLBCL. In order to attack chronic active BCR signaling therapeutically, we have initiated clinical trials in relapsed/refractory ABC DLBCL of ibrutinib, an irreversible and highly selective small molecule inhibitor of BTK. Thus far, ibrutinib monotherapy has induced many complete and partial responses, including "primary refractory" tumors that had never responded to any prior therapy. Given its excellent safety profile and selective mechanism of action, ibrutinib can be combined rationally with both chemotherapy and other signaling modulators to achieve cures for these patients, as will be discussed.