IV-4

Targeting B cell antigen receptor function in mature B cell neoplasms: opportunities, challenges and warnings

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Expression of several thousand B cell antigen receptor (BCR) complexes on the surface of individual mature B cells equips them with the unique capacity to recognize and respond in a highly-specific fashion to a multitude of environmental antigens. Through a complex network of effector molecules, the BCR transforms environmental signals into biochemical reactions responsible for highly codified cellular responses influencing survival, proliferation and terminal differentiation of B cells. Expression of BCR complexes is conserved in the majority of B cell malignancies arising from mature B cells. This, together with genetic and biochemical evidences showing constitutive BCR signaling in different types of B cell neoplasms has represented the rationale to introduce pharmacological inhibitors of BCR signaling into the clinical practice to treat several types of malignant B lymphoproliferative disorders. Nevertheless, our understanding of the specific contribution(s) of BCR expression, and signaling competence, to the malignant B cell behavior remains, surprisingly limited. In an attempt to fill this knowledge gap, we developed a mouse model ensuring close monitoring in vitro and in vivo of the effects of acute ablation of the BCR in highly-aggressive MYC-driven lymphomas. We could show that conditional BCR ablation did not, per se, prevent the outgrowth both in vitro and in vivo of receptor-less MYC lymphoma cells. Instead, strikingly, BCR loss impeded malignant B cells to effectively expand in tumor microenvironments shared with their BCR-expressing counterparts. Exploiting genomics, metabolomics and transcriptomics analyses we have started to elucidate the molecular networks under BCR control that ensure competitive fitness to malignant B cells. We also provide evidence that BCR-less malignant B cells can be spontaneously generated during tumor progression in several forms of human B cell lymphoproliferative disorders, establishing a possible Achilles heel of anti-BCR therapies. Finally, we report possible strategies enabling the clearance of BCR-less lymphoma cells, taking advantage of their acquired addictiveness to specific signaling pathways. Our results shed light on the coordinated regulation of signaling and metabolic networks imposed on malignant B cells by BCR expression/signaling, and provide indications for improved treatment options to fight several forms of mature B cell malignancies.