Btk antagonism diminishes pancreatic cancer growth via dual regulation of FcRγ and B regulatory cells

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Using a transgenic mouse model of squamous carcinogenesis, we previously reported that B cells foster the progression of solid tumors by depositing circulating immune complexes into neoplastic parenchyma thereby activating FcRγ regulated pro-tumoral myeloid phenotypes that diminish the chemotaxis of $CD8^+$ T cells. Accordingly, treating SCC-bearing mice with a B cell-depleting monoclonal antibody (αCD20 mAb) in combination with chemotherapy inhibits tumor growth; efficacy dependent on the presence of $CD8^+$ T cells. Human pancreatic ductal adenocarcinomas (PDA) also exhibit significant B cell residency and IgG deposition suggesting this cancer may too be susceptible to B cell-ablation as a therapeutic strategy. Orthotopic PDA tumor growth in mice genetically deficient in B cells or FcRγ was attenuated, however, αCD20 mAb monotherapy or with gemcitabine failed to reduce tumor growth. IL-10 expressing B regulatory cells were resistant to αCD20 depletion and were sufficient to restore PDA growth. Likewise, neutralizing IL-10R prior to gemcitabine therapy was effective at limiting tumorigenesis, again dependent on $CD8^+$ T cell immunity. Treatment with the small molecule Btk inhibitor, *Ibrutinib*, in combination with gemcitabine limited tumor burden by dual inhibition of BCR and FcRγ signaling, thereby simultaneously negating both B cell and myeloid cell mediated mechanisms of PDA development.