Section 1: Abstract Title

The potential role of STAT3 In the APE1/NF-kB regulatory axis in K-rasLSL.G12D/+;Pdx-1-Cre (KC) pancreatic tumor model

Section 2: Author Names

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Section 4: Abstract Body

APE1/Ref-1 (apurinic/apyrimidinic endonuclease-redox effector factor 1) is a multifunctional protein that has been shown to be overexpressed in multiple types of cancer. The overexpression of APE1/Ref-1 is linked to higher cancer cell survival and increased patient mortality. Furthermore, APE1/Ref-1 is a key regulator of transcription factors (TF) through redox signaling and protein-protein interaction. It is involved in proliferative and inflammatory signaling upregulated in cancer. Transcription factor NF-kB is involved in inflammatory cytokine expression and has been shown to be regulated by Ref-1. My project investigated how Ref-1 regulates NF-kB, specifically Rel-A, in a model using K-ras$^{LSL.G12D/+}$; Pdx-1-Cre (KC) pancreatic tumor cells (KC3590) derived from genetically engineered mice. Additionally, I explored other TFs within the APE1/Ref-1 signaling pathway, such as STAT3, in this model.

My work involved knocking down STAT3 levels within four variations of the KC3590 line. These were the KC3590/ΔNF-kB (parent) and KC3590/ΔNF-kB vector lines (vector) which contain exon deletions within the NF-kB gene rendering it nonfunctional. KC3590/13 and KC3590/15 are cell lines which are KC3590/ΔNF-B cells with functional full-length NF-kB added to the cells. Previous experiments demonstrated that the ΔNF-kB and ΔNF-kB vector lines are resistant to treatment by the specific Ref-1 inhibitors, including APX3330, which inhibit the redox signaling function of Ref-1.

Initial data demonstrated that adding back functional NF-kB to the NF-kB deficient cells reestablished sensitivity to APX3330, presumably due to the reintroduction of the Ref-1 target, NF-kB. Knockdown of STAT3 expression in the ΔNF-kB and ΔNF-kB vector lines demonstrated some sensitivity to APX3330, however, in the C13/15 cell lines, no enhanced sensitivity was observed. These data support the hypothesis that NF-kB is the major TF driving the growth of KC pancreatic tumor cells. Subsequent studies will clarify further the role of APE1/Ref-1 regulation in the KC model and the relative importance of APE1/Ref-1's target TFs.