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INTRODUCTION & OBJECTIVES: Interleukin-15 (IL-15) has been identified as a potent cytokine that activates the immune effector cells: CD8 T, natural killer (NK) and natural killer T (NKT) cells, which are important in cancer immunosurveillance. Further, IL-15 was selected from a large panel of cytokines as the only agent that can expand effector populations in the presence of prostate tumour cells. Due to these effects, there is potential for use of IL-15 in prostate cancer immunotherapies. Previously IL-15 has been shown to expand CD8 memory T cells by increasing activity of telomerase, an enzyme that extends telomere length, thus preventing cell senescence. Here we investigate the hypothesis that IL-15 expands NK and NKT cells in addition to CD8 T cells by increasing their lifespan and concomitant telomerase expression.

MATERIAL & METHODS: Peripheral blood mononuclear cells (PBMCs) were incubated with increasing concentrations of IL-15 for 7 days. Expansion of CD8 T, NK and NKT cells was determined by staining the non-adherent PBMCs with fluorophore conjugated antibody markers followed with analysis by flow cytometry. The effect of IL-15 on cell lifespan was investigated using the intracellular binding molecule carboxyfluorescein succinimidyl ester (CFSE) to measure cell doubling. Telomerase expression was investigated by staining cells with anti-telomerase reverse transcriptase (anti-TERT). TERT expression has previously been shown to correlate with telomerase activity. To confirm whether IL-15 was expanding cells through telomerase activation, we examined their expansion in the presence of IL-15 after the addition of the telomerase inhibitor BIBR 1532. Statistical analysis of results was carried out by one-way ANOVA and post-hoc Dunnett’s multiple comparison tests.

RESULTS: Increased cell expansion occurred with a 10-fold increase in NK cells using 25ng/ml IL-15 (n=5; p=0.0008), a 2-fold increase in CD8 T cells with 100ng/ml IL-15 (n=5; p=0.0378) and a 20-fold increase in NKT cells at this IL-15 concentration (n=5; p=0.0001). Telomerase expression also increased with rising IL-15 concentrations, with a 2-fold increase in CD8 T cells (n=5, p=0.0079), and a 5-fold increase in NK and NKT cells (n=4; p=0.0416 and n=4; p=0.0453, respectively) using the above concentrations. This corresponded to an 2-3 fold increase in cell doubling (lifespan) as measured by CFSE. The blocking of telomerase function by BIBR 1532 negated this IL-15 dependant expansion in all three of the cell types (n=5).

CONCLUSIONS: IL-15 expands CD8 T, NK, and NKT cell populations by increasing their lifespan. This is associated with an increased expression of telomerase in these cells. Inhibition of telomerase activity negates these effects indicating that this is a major mode of action of the cytokine. This finding indicates that any potential use of IL-15 in cancer immunotherapeutics should not be in combination with telomerase inhibitors, which are a class of drug gaining popularity as anti-cancer drugs.