IL-33 expression and Cancer

I. Introduction to current knowledge of cancer and IL-33
   A. The immune system is efficient and responsive at attacking cancer cells in primary tumors.
      1. In metastatic tumors the immune system is unable to recognize cancer cells.
   B. Cancer cells evolve as they replicate, as this study showed, they lose the ability to produce the protein IL-33.
   C. Without this protein the immune system cannot see the malignant cancer cells and this allows for further metastasis.
   D. This study observes the role IL-33 has in alarming the immune system in metastatic tumors.

II. IL-33: Interleukin 33 is protein produced in various parts of the body.
   A. It has two cellular purposes, one is intracellular and the other is extracellular.
   B. In this study, the extracellular function of IL-33 is important because it coordinates immune defense.
   C. There has been controversy on whether IL-33 acted as immuno protective or tumor-promoting.
      1. This study proves that IL-33 acts to alarm immune system in metastatic tumors.

III. Known (from results) : The correlation between IL-33 and MHC-I is very important in this study.
   A. IL-33 expression is decreased in metastatic carcinomas.
      1. Carcinoma is a cancer originating in the epithelial tissue on skin or lining of internal organs.
         a. This would include liver cancer, lung cancer, prostate cancer, etc.
      2. IL-33 expression was reduced in metastatic tumors compared to primary tumors.
      3. This reduction was present in both murine (affecting mice) lung and prostate as well as human prostate carcinomas.
   B. IL-33 and MHC-I are correlated.
      1. MHC-I is major histocompatibility complex, this complex is a set of cell surface proteins which bind to peptide fragments of the foreign intruder, in this case cancer cells, and display them on the cell surface.
      2. This mechanism allows the immune system to track intruders by scanning cell surfaces.

IV. IL-33 expression reverses the lack of MHC-I and alarms immune system of metastatic tumours.

1. The reduction of MHC-I expression is an indicator of rapid tumor growth. Since MHC cannot display malignant cancer cells and does not trigger immune response, metastasis continues.
2. Researchers found that IL-33 works to restore MHC-I expression in tumors.
3. Using murine lung carcinoma, metastatic cell lines were transfected with IL-33. This group showed a higher number of MHC on cell surface than the metastatic cell line alone.
4. This was done *in vitro*.

V. Hypothesis: Inducing IL-33 would increase MHC-I expression in metastatic cancer cells and in turn, slow tumor growth *in vivo.*

VI. In order to test this hypothesis a study on mice was conducted.
- A. The experimental group was injected with an A9 metastatic cell line transfected with IL-33
- B. The positive control was injected with A9 metastatic cell line only.
- C. The negative control was injected with TC1 primary tumor cells.
    1. The TC1 tumor cells are not genetically programmed to spread far, they grow locally.
- D. Green fluorescent protein (GFP) was added to track green tumor cells from site of origin.

VII. Results
- A. The experimental group (A9 +IL-33) showed a 30% - 45% lower tumor growth rates than the positive control (A9 alone). Both still higher than negative control.
- B. Mice injected with A9 suffered significant weight loss, tumor ulceration, and bleeding in surrounding tissue.

1. A9 + IL-33 as well as TC1 mice maintained weight and evidence of ulceration and bleeding was not present.
- C. The most important factor was the spread of the cancer cells or (CTCs) circulating cancer cells.
    1. The mice injected with A9 tumor cells had highest percentage of GFP positive CTCs in the liver with up to 32% and the adrenal glands contained up to 16%.
    2. Mice injected with A9 + IL-33 had ~0.15% CTCs in liver and ~2.63% CTCs in adrenal glands.
    3. No CTCs were found in the negative control since they are not genetically programmed to spread to distant tissues.

VIII. Study (human): A study to test whether IL-33 decreased tumor growth rate in human specimens.
- A. The researchers examined IL-33 expression in 342 human prostate cancer samples obtained at prostatectomy.

B. In order to test whether IL-33 is associated with reduced tumor growth rates, the researchers examine the recurrence of cancer in patients who had resected metastatic tumors.
    1. This would measure the time elapsed for recurrence of cancer after the prostatectomy
C. The results were as follows.
    1. Patients with low IL-33 expression had recurrence ~56.7 months
    2. Patients with high IL-33 expression had recurrence of around 97 months
D. This suggests that low IL-33 expression is associated with the spread of cancer and reduction time of recurrence.

IX. Conclusion

A. IL-33 expression is associated with the spread of cancer.
B. The addition of IL-33 to the cancer cell can modify its expression.
C. *In vivo* IL-33 can decrease tumor growth rate.
D. Induction of protein IL-33 restores immune response against metastatic tumors as found in mice and human specimen studies.
E. The finding can lead to new form of cancer treatment with the introduction of IL-33 to restore immune response.
    1. Allows immune system to combat cancer itself.