Immunogenetic Hypothesis for Cancer Survival: Genetics review and Immunological Evaluation of 200 Breast cancer patients at NCCC

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ABSTRACT

Session PO.IM02.13 - Immune Mechanisms Invoked by Therapies 2

2251 / 4 - Analysis of cancer survival using peripheral blood immunological parameters

Presenter/Authors

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Genetics review as reported at AACR2019

We have analyzed two gene segments (MHC HLA class I ligands and NK receptors), and each with single amino acid differences, that together can identify long survivors. Homozygosity of HLA–Bw4 supertype in HIV progression has been described. Since HLA-KIR genetic interactions of HLA-Bw4 with KIR (3DS1) only included Bw4, with the exception of B*27 and B*44 that use different mechanism of protection on the clinical outcome of HIV infection; NK–ligand interactions (NKG2A-HLA-E with HLA class I leader peptides) to explain the long term non-progressors (LTNP) to AIDS. HLA-B alleles have Methionine (Met) or Threonine (Thr) (at second position (P2) of their leader peptide.HLA-Bw4 alleles, with exception of B*38, encode leader peptide, with Thr at P2 and HLA-Bw6 encode Met at P2 are B*07, B*08 and B*14,all others have p2 Thr. Comparisons of the Thr in LTNP with progressors up to 15 years with non-infected Caucasian controls were significant. Also, aged Mexicans demonstrated significant increase of homozygosity of p2 Thr and Mexican patients with metastatic mammary cancer were studied after 10 years of treatment with surgery and chemotherapy; 39 survivors demonstrated significant increase of homozygosity of the p2 Thr compared to controls without cancer and 37 non survivors.

The purpose of tthe present study is to use Immunological Evaluation of Peripheral Blood NK cell number to predict survival in the War of the Immune System against cancer. Comparison of the two survival curves starts with the null hypothesis : there is no difference between the top 50% NK vs bottom 50% NK survival curves. P value is derived from Test Statistic found using log rank test. Breast cancer patients and colon cancer patients were evaluated. Both showed statistically significant differences in survival based on NK Cell number. Eight breast cancer patients had local radiation which showed in every one that the peripheral blood NK cell number decreased during radiation and returned to baseline values after radiation ended. In colon cancer patients the level of quantitative IgM and IgA defined a difference in overall survival. This was not the case for breast cancer patients. Survival was evaluated over a 9+ year period in a single California practice.

Genetics Review

Data presented at ASCO 2019

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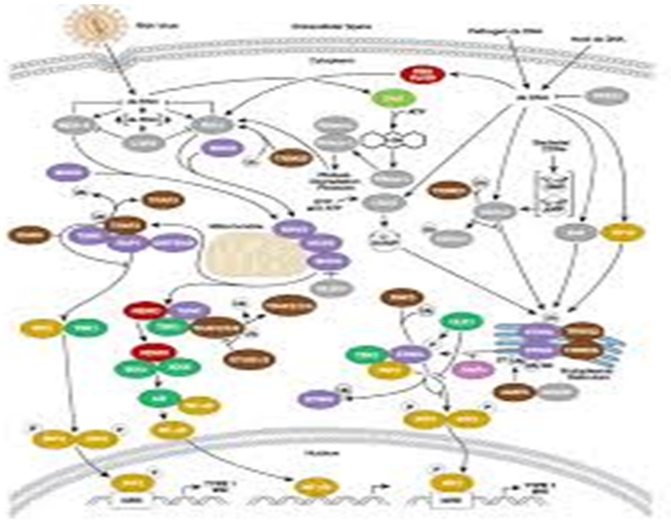
INTRODUCTION

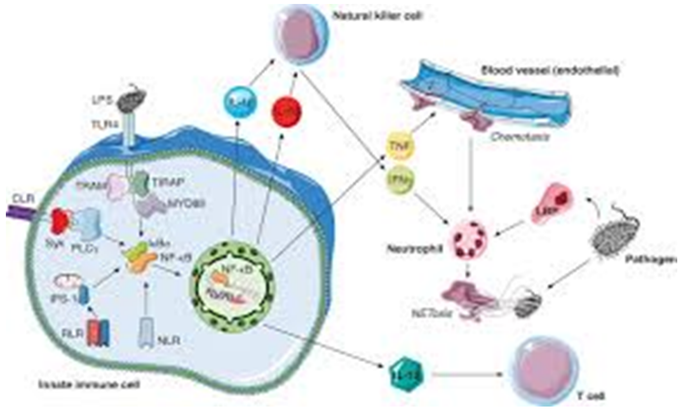
The purpose of the present study is to use Immunological Evaluation of Peripheral Blood NK cell number to predict survival in the War of the Immune System against cancer. Comparison of the two survival curves starts with the null hypothesis : there is no difference between the top 50% NK vs bottom 50% NK survival curves. P value is derived from Test Statistic found using log rank test. Breast cancer patients and colon cancer patients were evaluated. Both showed statistically significant differences in survival based on NK Cell number. Eight breast cancer patients had local radiation which showed in every one that the peripheral blood NK cell number decreased during radiation and returned to baseline values after radiation ended. In colon cancer patients the level of quantitative IgM and IgA defined a difference in overall survival. This was not the case for breast cancer patients. Survival was evaluated over a 9+ year period in a single California practice



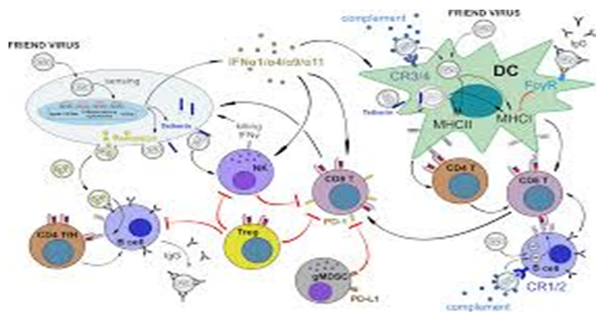
The immune system is complicated. There are many different genes which codes for unique protein sequences that combine with targets. These targets are variously termed antigens, epitopes, receptors, combining sites, etc. Each one is distinct at the at the level of amino acids in proteins or complex carbohydrate structures. The whole system can be divided into innate (non-specific) and adaptive (specific)

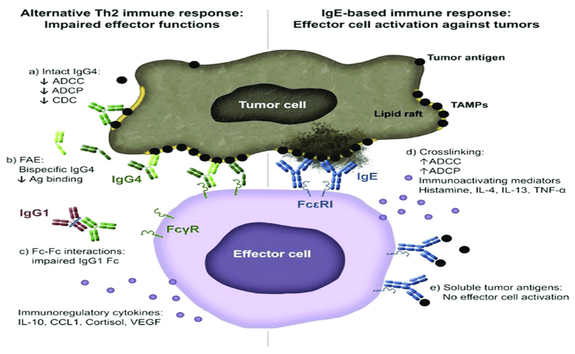
Innate Immune System

The innate immune system is composed of a number of different cell types



Immunity is innate (nonspecific) and adaptive (specific)





Survival duration (months) of 200 unselected breast cancer patients evaluated by natural killer cell numbers at the first visit to the Northern California Cancer Center

Figure 1. Median Groups

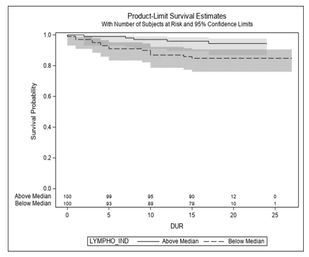
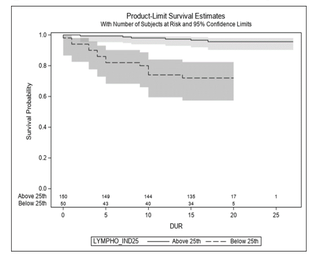
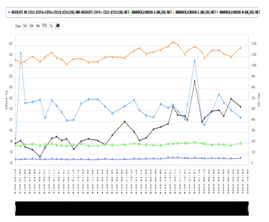


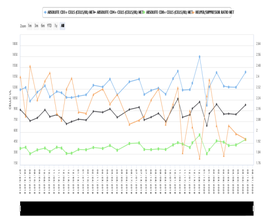
Figure 2. 25 th Percentile Groups



Detailed immunological analysis including cell subsets and antibody levels is done on all NCCC patients. The finding of substantial survival differences based on NK cell numbers is based on the initial measurement done at the first visit. Other cell types and even some Ig levels are predictive of survival, but none of the differences are as dramatic as that with NK cell number. Data from two HR+ metastatic breast cancer patients, one with multiple treatments and the other in a sustained complete remission with a taxane alone, are illustrated here

Patient A.S. ER/PR neg, Her2 positive mastectomy node negative, bone lesions by MRI, PET, and bone scan. Treatment trastuzumab and nab-paclitaxel, aromatase inhibitor and bisphosphonate. PET/CT was normal after 2 years and this was maintained at 5 years.





Patient A.N. ER/PR positive Her2 neg, infiltrating ductal carcinoma with papillary features with liver metastases at diagnosis. Treatment with nab-paclitaxel, radiation to primary, aromatase inhibitor subsequently added carboplatin and nivolumab.

Extensive statistical analysis, still underway, shows that treatments like radiation, chemotherapy, and immunotherapy cause changes in the numbers of cells. For example, radiation results in dramatic decreases in the number of NK cells, but this number returns to baseline or above a few weeks after radiation is completed. This effect must be a change in the traffic of NK cells, presumably to the radiated area, but this has not been formally proven. The multiple factors responsible for this phenomenon are under study. Also, there are numerous interventions, including natural substances, that can increase the numbers of NK cells in patients undergoing cancer treatments.

Conclusion

We have integrated decades of data from basic studies of genetics and immunology in mice into a translation clinical research program including measurements of cell numbers and molecules. These are all tests done by commercial laboratories. Observations can thus be utilized to treat patients anywhere. This is our ImmunoRegulatory approach to extending survival in patients with cancer.