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Meeting abstract

Breast cancer vaccines: maximizing peptide-based vaccines by regulatory T cell depletion and toll-like receptor 9 activation

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Background

Breast cancer is the most prevalent cancer in the world due to high incidence and favorable prognoses. Relapse is the major cause of mortality and will occur in up to 65% of patients with node-positive disease. Thus, effective long-term protection strategies are needed for preventing relapse. One approach that has generated interest in recent years is cancer vaccines. One of the problems with the translation of cancer vaccines is that multiple boosters are required in order to generate high-avidity memory immunity that is able to recognize naturally processed antigens. Our goal in this study was to determine if the need for boosters could be eliminated by preconditioning the immune system with anti-CD25 antibodies, which is known to deplete regulatory T cells, the latter of which are known to regulate the development of high-avidity memory T cells.

Materials and methods

We first developed a single peptide vaccine to generate neu-specific CTL immunity in the Neu-T mice. Neu-T mice have targeted expression of the activated rat neu in breast tissue that occurs at 3–4 weeks of age, and these mice develop spontaneous breast tumors at 15–17 weeks.

Results

The vaccine peptide, TYVPANASL (p66–74), was predicted by the SYFPEITHI algorithm http://www.syfpeithi.com to bind to mouse MHC class I, H-2d and was admixed with IFA and CpG. In the non-tolerant, Balb/c mice, vaccination prevented tumor development with only a single immunization. In the tolerant neu-T mice, the same vaccine succeeded in preventing spontaneous and transplanted tumors but only when given with repeated boosters. The response was durable as it was found that 80% of mice remained tumor free by week 45 of age. In order to determine if CD25+ Tregs may be preventing or regulating the development of high avidity memory immunity, anti-CD25 monoclonal antibodies were used to deplete Tregs prior to immunization. Following depletion, a single vaccination administered at week 10 following birth, when diffuse atypical hyperplasia is already evident in the mammary glands, vaccination induced a sufficient CTL response that has kept 100% of Neu-T mice tumor free until week 31. Immune monitoring revealed that Treg depletion resulted in higher avidity T cells following a single immunization.

Conclusion

Our results show that by combining a strong adjuvant (CpG) and an immunogenic peptide, we can induce an immune response capable of preventing spontaneous tumors when repetitive vaccinations are administered. Importantly, the need for boosters is reduced when Tregs are depleted prior to immunization. Removing or reducing the need for booster immunizations may facilitate the clinical translation of cancer vaccines for prevention of breast cancer development and relapse.