We currently are unable to identify pre-diagnostic tumor in women which are essential for a preventative vaccine cancer vaccine (2,6,7). TgMMTV-neu and C3(1)Tag mice are immune competent mammary tumor models that are genetically similar to human luminal B and triple negative breast cancer (4). Like triple negative breast cancer, tumors in C3(1)Tag mice develop earlier and grow more rapidly than TgMMTV-neu tumors. C3(1)Tag tumors also have an increased CD8+/CD4+ ratio (p<0.05) similar to human triple negative tumors (1). Using SEREX and natural protein arrays, we identified 55 pre-invasive antigens that were present in mice that would develop cancer but not parental control mice.

The goal of this study was to identify pre-diagnostic antigens in transgenic mouse mammary tumor models that are functionally relevant in human breast cancer survival to develop a preventative breast cancer vaccine.

Methods:

Mouse Sarcoma Collection: TgMMTV-neu and C3(1)Tag mice were bred under specific pathogen-free conditions. Tumor samples were collected using the model from loss of mammary gland 

Figure 1: Knockdown expression of targets decreases cell survival and increases apoptosis when characterized to mock control in at least one of the two human breast cancer cell lines. Confirmation assays of targets.

Figure 2: Vaccination with peptides for each of the targets significantly inhibit tumor growth in both the HER2 and triple negative mouse mammary tumor models compared to PBS. Decrease in tumor volume (p<0.05) across all timepoints was calculated with ANOVA using the Bonferroni post-hoc test.

Figure 3: Pre-diagnostic targets identified by siRNA knockdown inhibited tumor growth in both TgMMTV-neu and C3(1)Tag mice.

Figure 4: Pre-diagnostic antigen peptides are immunogenic by IFN-g ELISPOT in TgMMTV-neu mice.

Conclusions:

The tumor antigen repertoire changes as tumors progresses, therefore for preventative vaccines against the earliest stages of tumor development need to be identified. Five pre-invasive antigens (VP535, ARPC2, SERBP1, PDI6, and KRT8) identified from the TgMMTV-neu and C3(1) Tag mouse mammary tumor models were essential for cell survival and apoptosis prevention in human breast cancer cell lines. All of the antigens except ARPC2 inhibited tumor growth in both TgMMTV-neu and C3(1)Tag mice.

Transgenic mouse mammary tumor models are good surrogates to identify breast cancer initiating targets suggesting that pre-invasive antigen targets recovered in mouse may also be important in human breast cancer.

Future studies will evaluate the use of vaccines containing epitopes from several of these antigens to prevent spontaneous tumors in these mouse models.

References:


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