A COMPARISON OF CANCER TESTIS ANTIGEN EXPRESSION IN DIFFERENT CANCERS

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Abstract. Aim: The purpose of this note is to show that the fraction of patients whose tumors express cancer testis antigens (CTA) varies according to the location of the cancer.

Methods: Gene expression data from TCGA for 20 different cancers was analyzed for expression of GAGE, MAGE, XAGE, SSX, and NY-ESO-1 family genes.

Results: The rates of CTA expression varied from about 5% (kidney KICH) to 100% (prostate cancer). High levels of CTA expression are found in bladder, lung cancer, prostate, testicular, and uterine sarcoma cancer.

Conclusion: The clinical effects or prognostic value of CTA expression may also vary significantly with tumor location.

Introduction. This is a rough working draft.

Cancer testis antigens (CTAs) are products of several classes of genes that are normally expressed only in the testis and uterus (germ cells and placenta). Outside of these locations, expression of CTA proteins is normally repressed. However, many malignant tumors also express CTAs. Expression (actually derepression) of CTAs in tumors is controlled by epigenetic methylation. Summaries of the biology of CTAs in cancer may be found in Whitehurst [1], Kim et al. [2], Salmaninejad et al. [3], Fratta et al. [4], and Rajagopalan et al. [5]. There is a website serving as a database for information related to CTAs, maintained by the Ludwig Institute (http://www.cta.lnce.br).

In bio-informatics terms, the CTA genes represent a strong signal in cancer mRNA expression data. In each patient, each of the several hundred CTA genes is either turned off (zero expression) or on (significant expression). Each tumor expresses none, one, or many CTAs, in patterns we do not understand. In reality, it is worse: Gjerstorff et al. [6] showed that “Significant intercellular and subcellular differences in GAGE protein levels were observed, and most GAGE-positive tumours..."
also contained cancer cells lacking GAGE expression.” The same type of variation may well occur for other CTAs.

The role of CTAs in cancer is not well understood. Are they immunogenic or tumorgenic or both? Are they suitable drug targets? Can they be used as prognostic biomarkers? Drug trials using MAGE for immunotherapy were not particularly successful. Some positive results are reported in [7, 8, 9, 10].

Most studies of CTAs have focused on a particular type of cancer. Here we want to compare CTA expression across different types of cancer. It would be better to correlate expression data with clinical outcomes, especially recurrence, but one thing at a time. Our limited expectations should be explicitly stated. There is a low probability of finding a suitable CTA drug target, but possibly if the right candidates could be identified. There is a slightly better chance of connecting CTA expression with outcomes in some cancers. But the real objective is only to understand what process in the tumor is reflected by CTA expression, i.e., to understand what is going on here, whether or not it is directly applicable, on the theory that understanding the disease process will in the long run help us fight it.

**Methods.** mRNA expression data for was obtained from The Cancer Genome Atlas (TCGA). Expression from tumor tissue was separated from normal adjacent tissue, and only the former was used here. For each of the 5 types of CTA considered here, a threshold for counting as expression was determined. The 5 types were the GAGE, MAGE, XAGE, SSX families and the NY-ESO-1 gene. Since there were very few subjects with nonzero low expression values, the results are not very sensitive to the threshold. Then for 20 different types of cancer, and the 5 CTAs considered here, the fraction of patients expressing at least one of those genes significantly was counted.

**Results.** There were huge differences, as shown in the table.

- High levels of CTA expression are found in bladder, lung cancer (adenocarcinoma and squamous cell), prostate, testicular, and uterine sarcoma cancer.
- Medium levels of CTA expression are seen in colon, colorectal, rectum, liver-HCC, stomach, cervical, ovarian, thyroid, and uterine cancer.
- Low levels of CTA expression are found in kidney cancer (KICH, KIRC, KIRP), pancreatic, and cholangiocarcinoma cancers.
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**Figure 1.** Expression rates for CTA genes in different types of cancer. Second-to-last column indicates fraction with one or more of the previous types, whereas last column indicates fraction of samples with none of these.

**Discussion.** It is probably fair to say that we don’t really understand all the factors that lead to CTA expression in tumors, in the sense of knowing which kinds of tumors tend to express which CTAs, and why. Neither are the effects of CTA expression well-understood. With that in mind, we can ask some more direct questions.

1. Why is there a lot of CTA expression in hepatocellular carcinoma (liver), and almost none in cholangiocarcinoma (bile ducts)? Our results contrast with Utsunomiya et al [13], who showed that in 20 tumors of intrahepatic cholangiocarcinoma, 10 (50%) expressed one of 5 CTAs considered (MAGE-1, MAGE-3, NY-ESO-1, SCP-1, SSX-4). Perhaps a larger number of samples would help resolve this. Most of the TCGA cases are intrahepatic, but the specific type may still be a factor. See [11, 12, 13].
2. Why is there no NY-ESO-1 expression (and some other CTAs not on our list) in prostate cancer?
3. Why does thyroid cancer have 2/3 SSX but almost nothing else?
Expand all the text. Do all 30 types in TCGA. Maybe more old references to CTA expression. Look for stage, grade, mnt, etc. variation. Look for clinical significance, especially recurrence. Look for implications or associations between CTAs. Which other gene sets should be included? What other genes are differentially expressed along with these, including CTAG2, CSAG1, TARDBP, others.

**CTA genes.** For this study we have used the following representatives of the class of cancer-testis antigens.

2. **MAGEA genes:** MAGEA10, MAGEA11, MAGEA12, MAGEA1, MAGEA2, MAGEA3, MAGEA4, MAGEA5, MAGEA6, MAGEA8, MAGEA9B.
3. **XAGE1D.**
4. **SSX genes:** SSX1, SSX2, SSX3, SSX4, SSX5, SSX6, SSX7, SSX8.
5. **CTAG1B (= NY-ESO-1).**

These choices were guided by the literature and our own investigations, but are still somewhat arbitrary.

1. **Declarations**

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**Authors’ contributions.** Nation, J. solely responsible for the paper.

**Data source and availability.** This research is based clinical and mRNA expression data for hepatocarcinoma, publicly available from The Cancer Genome Atlas (TCGA).

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**Conflicts of interest.** There are no conflicts of interest.

**Patient consent.** Not applicable.

**Ethics approval.** Not applicable.

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REFERENCES


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