Probabilistic model for cancer immunoediting

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Introduction

The question we are trying to answer is whether immune system fights cancer. This has a far reaching consequences for personalised therapy and immune therapy. The believed biological mechanism how immune cells recognises mutations in cells is graphically depicted in Figure 1. After a mutation occurs in a DNA, a new protein will be created when RNA copies the DNA segment. The new protein will be shredded into peptides. These new peptides will float among all the peptides in the cell. Some of the peptides bind to the membrane of the cell. The immune system cells are constantly checking the body for foreign proteins. If they detect that a cell has suspicious proteins, for instance, due to viral infection, it will kill the cell. Otherwise, a tumour develops when a cell accumulates mutations, stops performing its function and starts dividing.

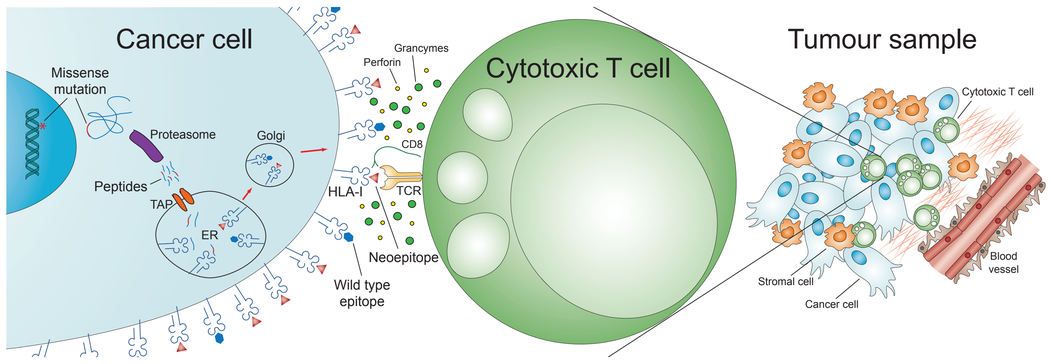

Figure 1: Illustration of the biological mechanisims of the immune system recognition of the mutation

DNA is made of nucleotides, namely A, T, C, G bases. Three nucleotides form a codon and codify for an amino acid. There are 20 amino acids and some different codons codify for the same amino acid.

We are investigating point mutations when one nucleotide is changed into another. We consider silent mutations which do not change the amino acid and missense mutations which change the amino acid and so changes the protein. It is believed that missense mutations are much more likely to be affected by the immune system and other tumour suppressor mechanisms.

We take into consideration driver and essential genes. Driver mutations give selective advantage while purifying selection occurs when a mutation in an essential gene causes the death of the cell.

Main Objectives

The main objective is to develop a robust model for predicting the number of mutations. We want to be able to evaluate the significance of immunoediting and identify the cases when immunoediting happens.

Hypothesis

Immune system is active and clears some of the mutated cells. If we observe fewer missense mutation than expected then there is negative selection either due to immune system or purifying selection.

Model

To begin with, we introduce a simple model. We assume that mutation rate is constant and when mutations occur there are constant probabilities for them to be silent or missense. The following equations follow straight away

$$\text{Expected } \#\text{ silent mutations} = \underbrace{q}_{\text{probability a mutation is silent}} \times \underbrace{u}_{\text{mutation rate}} \times \underbrace{t}_{\text{time}}$$

$$\text{Expected } \#\text{ missense mutations} = \underbrace{p}_{\text{prob. mut. missense}} \times \underbrace{u}_{\text{mut. rate}} \times \underbrace{t}_{\text{time}} \times \underbrace{(1-\beta)}_{\text{probability cell survives}}$$

Here we have included the probability that a missense mutation might be recognised by the immune system or it might effect the essential gene and kill the cell. Furthermore, taking the ratio of these equations we obtain the expected ratio which we can compare with the observed ratio.

$$\text{Expected } \frac{\#\text{ missense mutations}}{\#\text{ silent mutations}} = \frac{p}{q}(1-\beta)$$

We have estimated p and q probabilities based on

- Genetic code (amino acid relation to nucleotides)
- Codon distribution
- Signatures and / or spectrum (codon susceptibility to mutation)

Results

The model fits to the data very well. The linear regression for the ratio of the number of silent over missense mutations for some tumour types was very close to the expected ratio. We have repeated the analysis by not excluding driver genes but there was little difference.

We have computed the ratio of observed and expected numbers of silent per missense mutations for each sample and presented the data in Figure 2. The model predicts that more depleted samples to the left from 1 are more likely to have been effected.

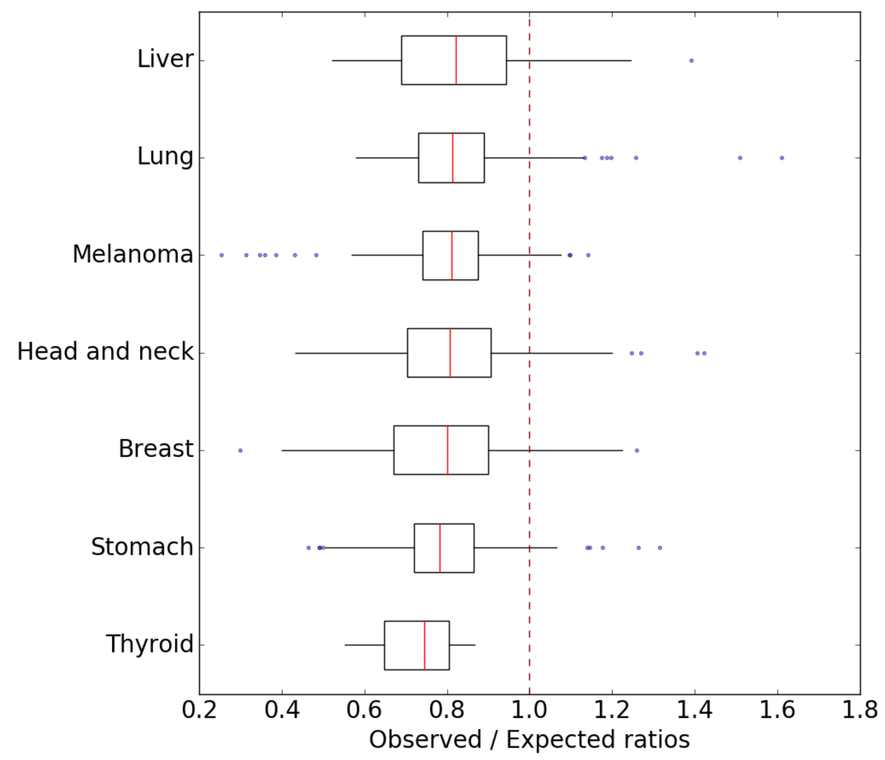

Figure 2: Observed over expected ratios of silent over missense mutations. Expected ratio is computed using the model by incorporating sample specific signatures.

Conclusions

We have observed negative selection, although the proportions of immunoediting and purifying selection are unknown. The observed depletion for different tumour types varied and since purifying selection should have the same effect we conclude that immunoediting is likely to be happening.

Further research

The most important research direction now is control sample selection and investigation. This would reveal if the model predictions were accurate. We are also extending the current model in several directions. Firstly, we are trying to incorporate more known information about the biological process to adjust the probabilities. Secondly, we are introducing more sophisticated mathematics to the model, mostly ideas from the population genetics.

References

Figure 1 was adapted from: Joyce JAand Pollard JW. (2009). Microenvironmental regulation of metastasis. Nat Rev Cancer 9, 239-252.