Alternative splicing as a putative mechanism of neoepitope generation in paraneoplastic neurological syndromes

Context

Paraneoplastic neurological syndromes (PNS) are rare auto-immune disorders that develop in patients with cancer and represent clinical manifestations of spontaneous antitumor immunity response targeting neuronal proteins expressed by tumour cells, e.g. so-called onconeural antigens (Ags). Both intracellular and membrane bound onconeural proteins have been identified and the presence of specific auto-antibodies (Abs) directed against these onconeural Ags in the serum and cerebrospinal fluid of patients constitutes key diagnostic biomarkers. Many tumours express onconeural Ags, but only a minority of patients with such tumours develop PNS, suggesting that additional mechanisms, besides Ag expression, are responsible for breaking down immunological tolerance and promotion of anti-tumor immunity.

Alternative splicing is a process that enables a mRNA to direct synthesis of different protein variants, called isoforms. It has been shown to be an important mechanism of neoantigen production in cancer cells. One hypothesis of the team is that alternative splicing plays a role in PNS, especially in the anti-Ri PNS. Indeed, the proteins targeted in the anti-Ri PNS are the NOVA proteins, which also regulate alternative splicing. We hypothesised that this mechanism could be implicated in neoepitope creation leading to immune tolerance breakdown that results in particularly intense and efficient antitumor immune attack.

Mission

We already generated tumour RNA-seq data for three types of PNS (including anti-Ri) and their matched control tumours. A preliminary analysis of the alternative splicing was done on these three dataset using one method.

The role of the student will be to:

- See if the use of other methods for alternative splicing are needed.
- Describing the common and specific alternative splicing events between the three PNS to identify mechanisms that can potentially lead to immune tolerance breakdown and later to PNS.

For these missions, the student will be supervised by a bioinformatician and a clinician/biologist, and he will be collaborating with a PhD student.

Location

The French reference centre on autoimmune encephalitis and paraneoplastic neurological syndromes, located in Lyon in the Pierre Wertheimer hospital, study the characteristics of these cancers associated with paraneoplastic neurological syndromes. Our research aims at determining the molecular specificities of these tumours compared to control tumours of the same type, and their roles in the breakdown of the immune tolerance and initiation of the auto-immune disease directed against the nervous system. To achieve these goals, we will combine genomic, transcriptomic and epigenetic high throughput approaches (e.g. DNA-, RNA-seq, and related methods) in collaboration with other teams in the BETPSY project (https://www.rhu-betpsy.fr/).

Profil

A Master 2 student, either a bioinformatician with knowledge and interest in the biology of cancer, or a biologist/clinician interested in data analysis, data mining, and programmation with some knowledge in R and potentially Unix.

Contact

Virginie Desestret: virginie.desestret@univ-lyon1.fr
Valentin Wucher: valentin.wucher@univ-lyon1.fr

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