

**Thèse Maria José Lista, 7 décembre 2016**

**Titre :** La nucléoline est impliquée dans le mécanisme d'évasion immunitaire basé sur la protéine EBNA1 du virus d'Epstein-Barr et représente une cible thérapeutique pertinente pour traiter les cancers liés à ce virus

**Titre :**

Nucleolin is involved in Epstein-Barr virus EBNA1-based mechanism of immune evasion and represents a relevant therapeutic target to treat cancers linked to this virus

**Abstract :**

The Epstein-Barr Virus (EBV) is the first oncogenic virus described in humans. It is a ubiquitous virus which infects over 90% of the human population.

EBV causes a latent infection of B lymphocytes and remains asymptomatic in most of infected individuals. However, in some conditions like immunosuppression, EBV can cause uncontrolled cell proliferation responsible for some types of cancers like Burkitt lymphoma, Hodgkin lymphoma and nasopharyngeal carcinoma.

During latency, EBNA1 is the only protein expressed in all EBV-infected cells as it is essential for EBV genome replication and maintenance. EBNA1 is highly antigenic and T cells raised against EBNA1 exist; nevertheless EBV-infected cells are not eliminated by the host immune system. This is due to the central GAR (Gly-Ala repeat) domain of EBNA1 which is able to inhibit the translation of its own mRNA in cis, thereby preventing the recognition of EBV-infected cells by the immune system of the host. The mechanisms involved in this GAR-based translation inhibition were unknown when I started my PhD.

During this thesis, we identified the first cellular factor, Nucleolin (NCL), able to affect GAR-based translation inhibition. We showed that NCL overexpression enhances EBNA1 translation inhibition and inversely, that its downregulation decreases EBNA1 translation inhibition effect. Furthermore, we demonstrated that the interaction between NCL and GAR RNA occurs through NCL binding to GAR-encoding mRNA via a particular secondary structure called G-quadruplex (G4). We showed that disrupting NCL-GAR RNA interaction with small G4 ligands enhances EBNA1 translation and thus antigen presentation, which constitutes a new therapeutic avenue to treat EBV-associated cancers. Finally, we went deeper into the mechanism involved in this interaction by showing that NCL has a direct effect on the GAR-based translation inhibition and that the nuclear location of NCL-GAR RNA interaction is forced by the nuclear location of NCL in the cells.

Taken together, these results have shed light upon the mechanism involved in the GAR domain translation inhibition and immune evasion, and have revealed a possible therapeutic target to eradicate EBV-associated cancers.