Regulation of immune checkpoint expression

Don-Marc Franchini¹, Olivia Lanvin¹, Marie Tosolini¹, Emilie Patras de Campiano², Sarah Péricart¹, Morgane Lebras¹, Cédric Rossi¹, Anne Cammas¹, Laetitia Ligat¹, Frédéric Pont¹, Paola B. Arimondo³, Camille Laurent¹, Fabien Despas², Maryse Lapeyre-Mestre², Stefania Millevoi¹, Jean-Jacques Fournié¹

¹CRCT, INSERM U1037, Toulouse, France
²Medical and Pharmacoepidemiology Research Unit, INSERM U1027, Toulouse, France
³Epigenetic Targeting of Cancer, FRE3600 CNRS, Toulouse, France

Despite the clinical success of blocking immune checkpoint receptors such as programmed cell death-1 (PD-1) in cancer, the mechanisms controlling the levels of these therapeutic targets at the surface of effector lymphocytes have not been fully elucidated. In this study, we show that microtubule dynamics controls mRNA transport, translation and cell surface expression of PD-1. The underlying mechanism involves the PDCD1 mRNA interaction with tubulin-associated ribonucleoprotein complexes and its transport by KIF5B/KLC1 kinesin 1 to translating polysomes. In vitro and in vivo evidence from both healthy donor’s blood and tumor-infiltrating lymphocytes from Hodgkin’s lymphoma patients demonstrate that this mechanism controls the expression of PD-1, as well as of the co-inhibitory receptors LAG3, TIM3, and CTLA4 in the CD4⁺, CD8⁺ and γδ T cell subsets. Furthermore, disproportionality analysis of immune-related adverse events in patients under currently used microtubule-targeting drugs unveils a significant higher risk of autoimmunity. Our study identifies a regulatory pathway controlling immune checkpoint receptors expression simultaneously, which open an opportunity for new potential therapeutic targets discovery and for novel associations between chemotherapies and immunotherapies.