BAD-LAMP influences TLR9 signaling zone in human plasmacytoid dendritic cell and contribute to triple negative breast cancer immune evasion.

Plasmacytoid dendritic cell (pDC) stimulation of Toll-like receptors 7 and 9 (TLRs) by nucleic acids (NA) leads to high but transient production of type-I interferon (IFN-I), which in addition of its potent anti-viral role, is a critical mediator of tumor rejection as well as an inducer of autoimmunity. Human pDCs express a set of adaptor molecules that regulate their response to NA by determining the localization of TLR7 and -9 signaling complex mostly to avoid auto-immunity.

Our team has shown that the Brain And Dendritic cell Lysosomal Associated Membrane Protein (BAD-LAMP) (LAMP5) is expressed in cortical neurons of mice and human as well as being exclusively present in non-activated human pDCs and leukemic blastic pDCs neoplasms among hematopoietic cells. Our recent results indicate that in pDCs activated by synthetic CpG DNA, BAD-LAMP promote the trafficking of the TLR9/MyD88 complex from IRF7 toward NF-κB signaling endosomes and thus inducing a switch from IFN-I to TNF-α secretion.

Moreover, together with our collaborator, we have demonstrated that tumor-associated pDCs (TApDC) isolated from triple negative breast cancer (TNBC) showed an intermediate activated phenotype characterized by high BAD-LAMP expression that fail to produce IFN-I and are associated with poor breast cancer prognosis. Analysis on the TNBC supernatant reveal that TGF-β and TNF-α are responsible for the inhibition of type I IFN production and sustain BAD-LAMP expression by a yet unknown mechanism.

Recent unpublished data demonstrate that in steady-state pDC, BAD-LAMP is associated with the TLR-chaperone UNC93B1 that is responsible for stabilizing TLR7 and -9 in steady-state as well as being fundamental for their exit from the ER in activated human pDC. Intriguingly, the level of expression of UNC93B1 and BAD-LAMP influence their reciprocal localization demonstrating the existence of a unique regulatory complex that will be unrevealed by the analysis of BAD-LAMP interactome by mass-spectrometry and confocal/super-resolution microscopy. Finally, the concurrent presence of TLR9 ligand (stimulatory) together with the TGF-β and TNF-α (inhibitory) in the TNBC supernatant will be analysed using the breast cell line MDA-MB-231 as well as supernatant derived from tissue dissociated from TNBC patients.

Keywords : pDC, signaling endosome, TLR9, LAMP-5, Breast cancer
Authors :
References : , , ,

Authors

Leone Dario 1, Gatti Evelina 1, Pierre Philippe 1,

1. DC Biology, Immunology Center Marseille Luminy (CIML), Marseille, FRANCE