CD8⁺ T cell dysfunction mediated by ovarian carcinoma ascites: involvement of lipid metabolism

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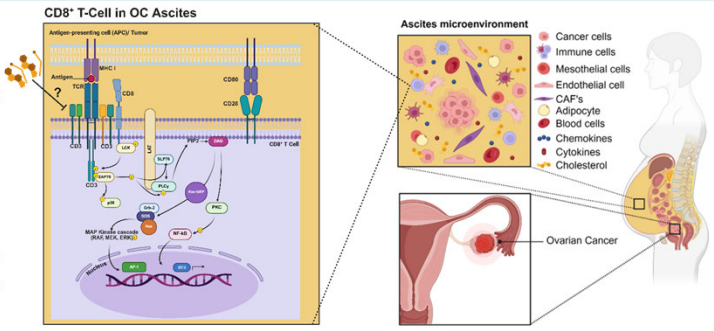
Introduction

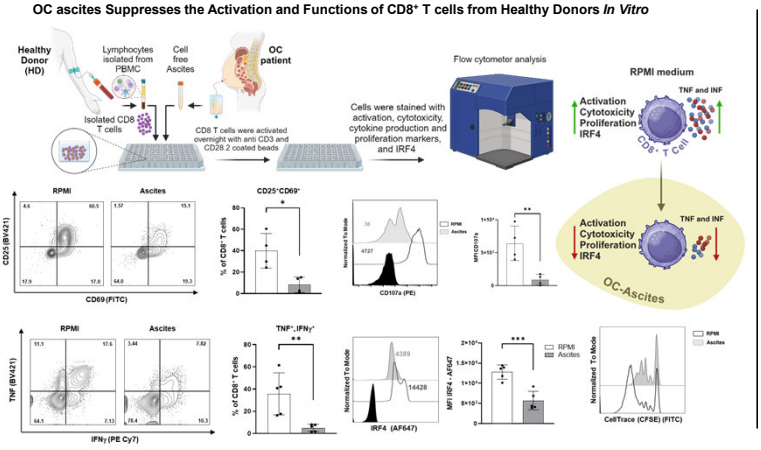
- Ovarian cancer (OC) is the deadliest gynecological malignancy, which at advanced stage is characterized by accumulating ascites.
- CD8⁺ Cytotoxic T Lymphocytes (CTLs), which produce IFNγ, TNF and cytotoxic molecules including perforin and granzymes display specific cytotoxicity and long-term memory against tumor cells.
- OC ascites is known to contribute to an impaired CD8⁺ T cell activation and proliferation.

→This study investigates the underlying mechanisms responsible for the impaired functionality of CD8⁺ T cells within the OC ascites microenvironment.

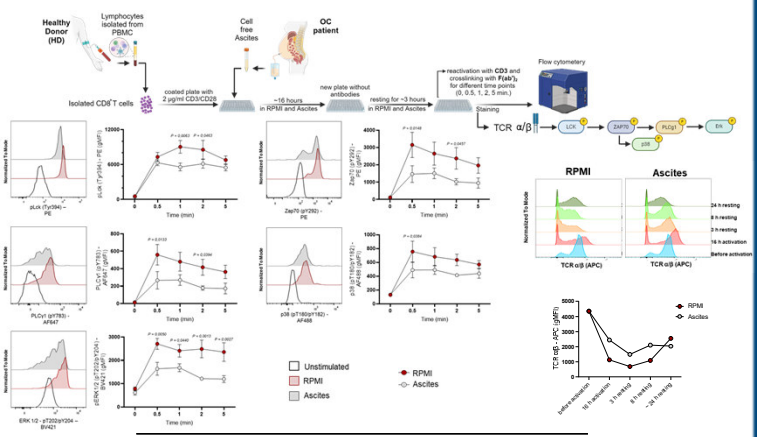


Results

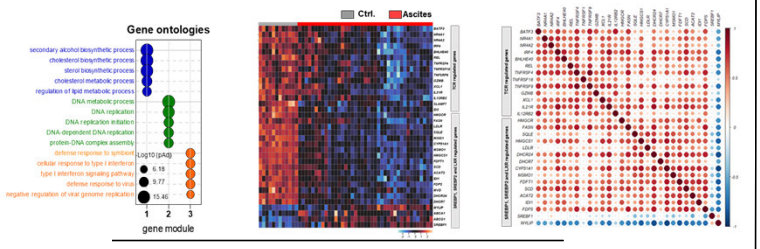
OC ascites Suppresses the Activation and Functions of CD8⁺ T cells from Healthy Donors *In Vitro*



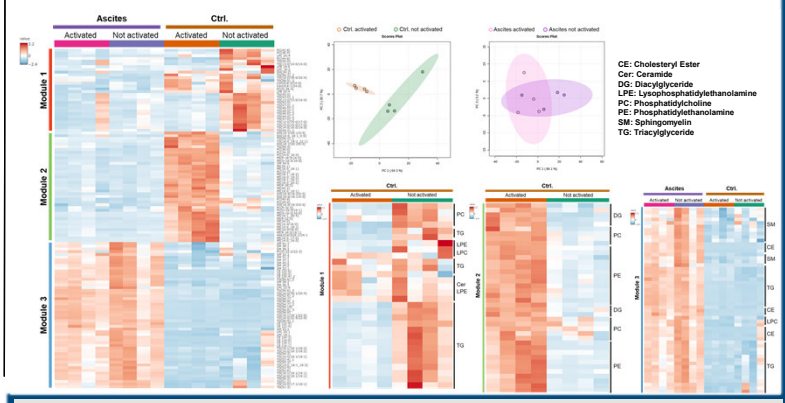
Supressed CD8⁺ TCR signaling and endocytosis in OC ascites



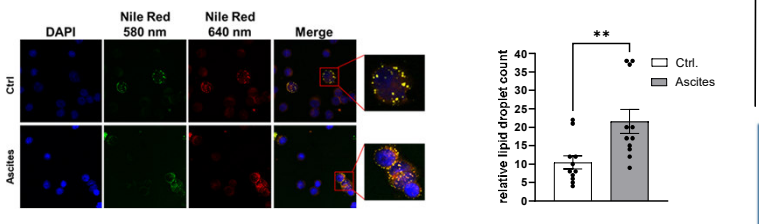
Cholestrol- fatty acid- biosynthesis and TCR signaling are downregulated in CD8⁺ T cells cultured in OC ascites



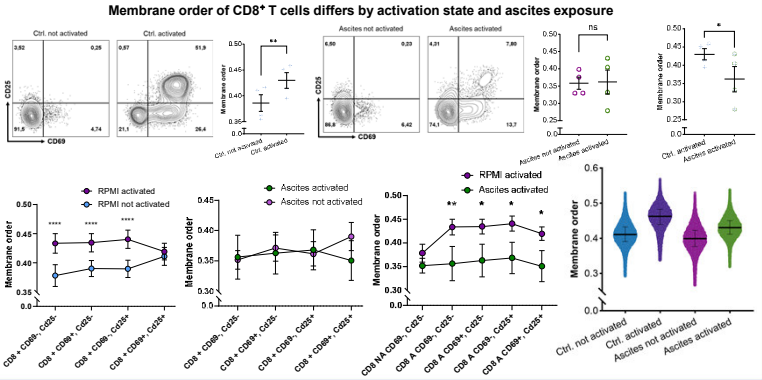
Lipidomics: increased CE/TG levels, while decreased PE/PC levels in CD8⁺ T cells cultured in OC ascites



Nile Red staining showed increased lipid droplets in CD8⁺ T cells cultured in OC ascites

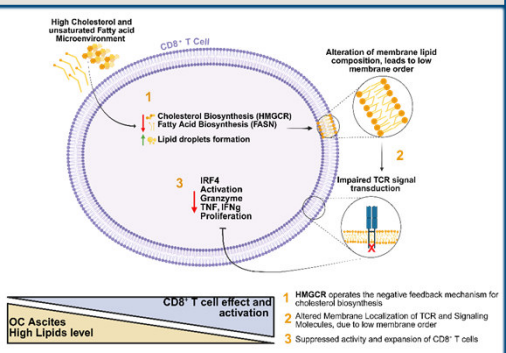


Membrane order of CD8⁺ T cells differs by activation state and ascites exposure



Conclusion

- OC ascites reduces CD8⁺ T cell activation, cytotoxicity, and production of TNF, IFNγ, and IRF4.
- FACS analysis reveals reduced phosphorylation of key proteins in the TCR signaling pathway in ascites.
- RNA-seq analysis shows downregulation of genes involved in cholesterol synthesis, fatty acid metabolism, and TCR signaling in ascites exposed CD8⁺ T cells.
- .Lipidomics analysis indicates that activated CD8⁺ T cells in ascites accumulate higher levels of cholesteryl esters (CE) and triacylglycerides (TG).
- Confocal microscopy reveals increased lipid droplet accumulation in CD8⁺ T cells activated in ascites.
- Membrane fluidity analysis using Pro12A probe shows that CD8⁺ T cells in ascites exhibit lower membrane fluidity compared to control, and that fluidity increases upon T cell activation.



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