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The inflammasome of tumor cells in colorectal cancer : a potential target to strengthen the Th1/Tc1 response of Tumor Infiltrating T lymphocytes (TILs)

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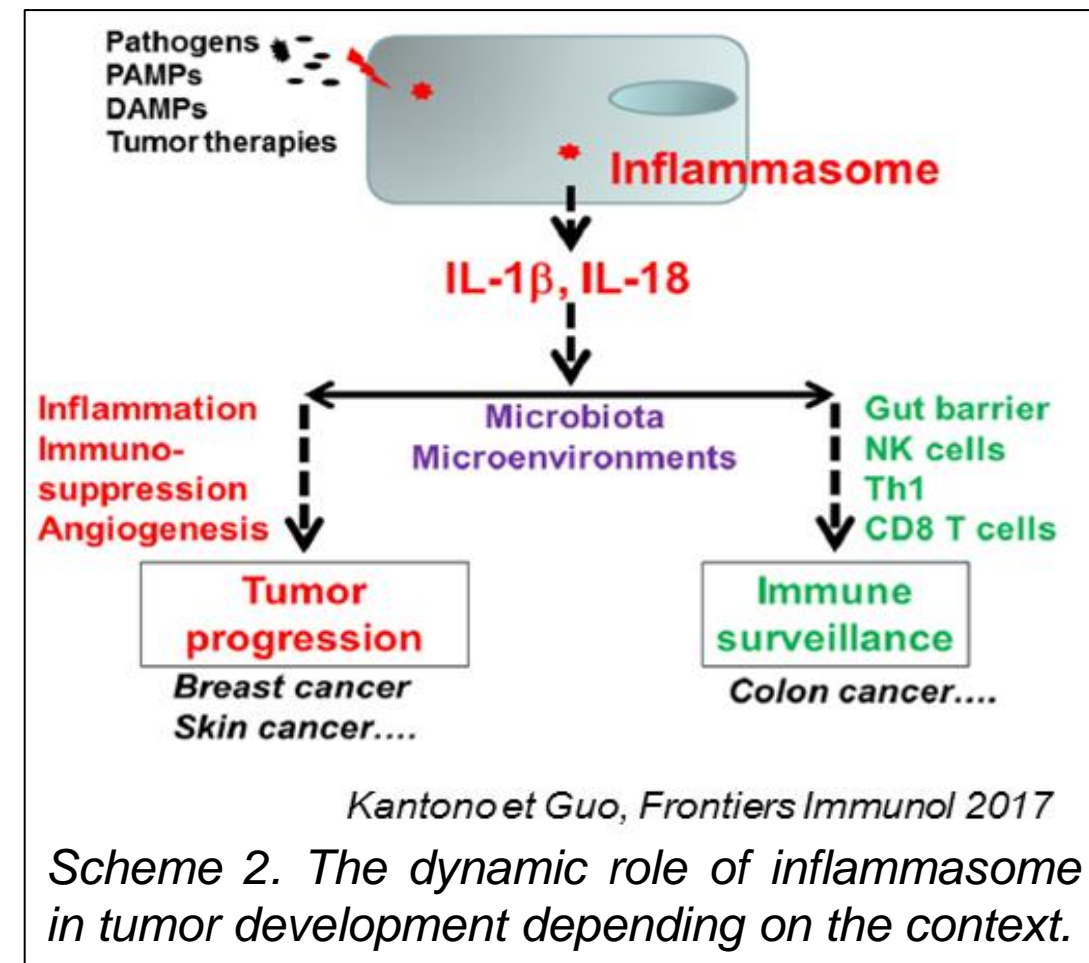
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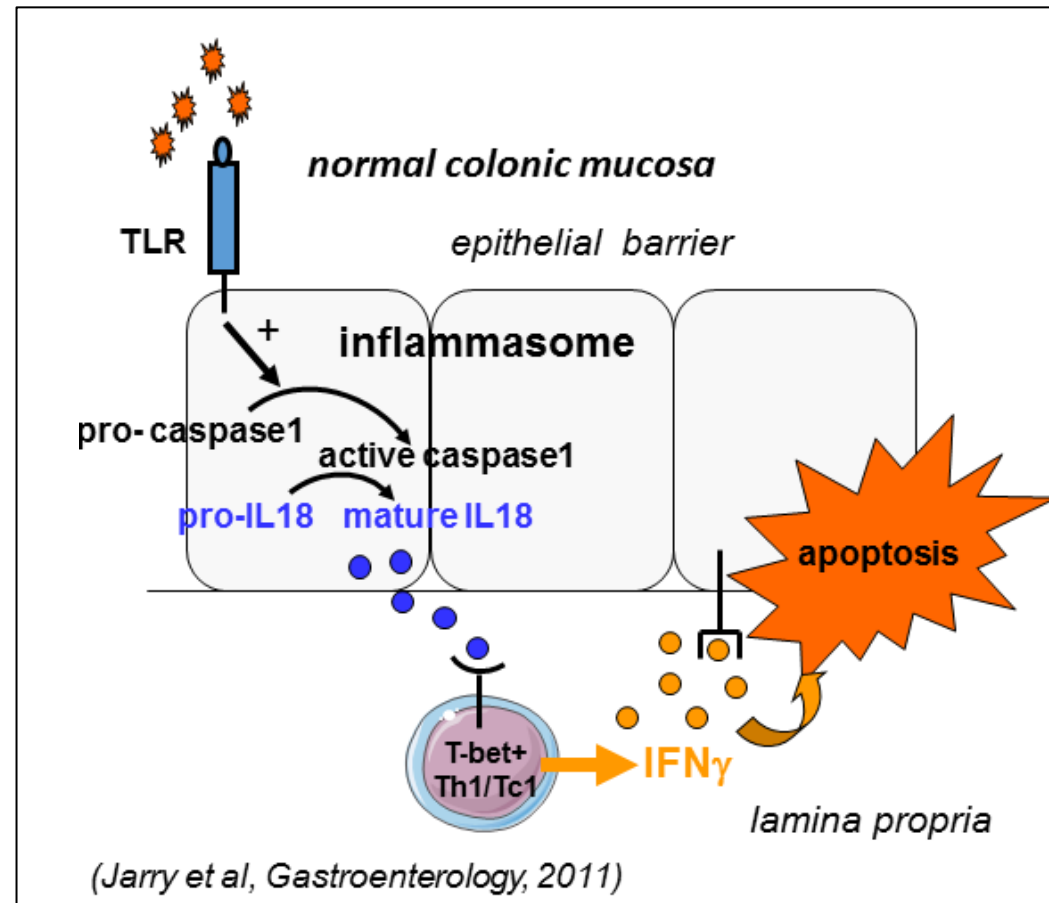
Background

The inflammasome is an innate immunity platform present in normal human intestinal epithelial cells, whose effector protein, caspase-1, can rapidly mature IL-18 and generate a mucosal Th1/Tc1 (IFN γ) response (scheme 1). The role of the inflammasome in cancer remains elusive and controversial. Indeed, it can promote or inhibit tumor progression, depending on the context and organ (scheme 2). In colon carcinogenesis, the inflammasome is mainly studied in mouse models of colitis-associated cancer, a clinical entity distinct from human sporadic colorectal cancer (CRC).

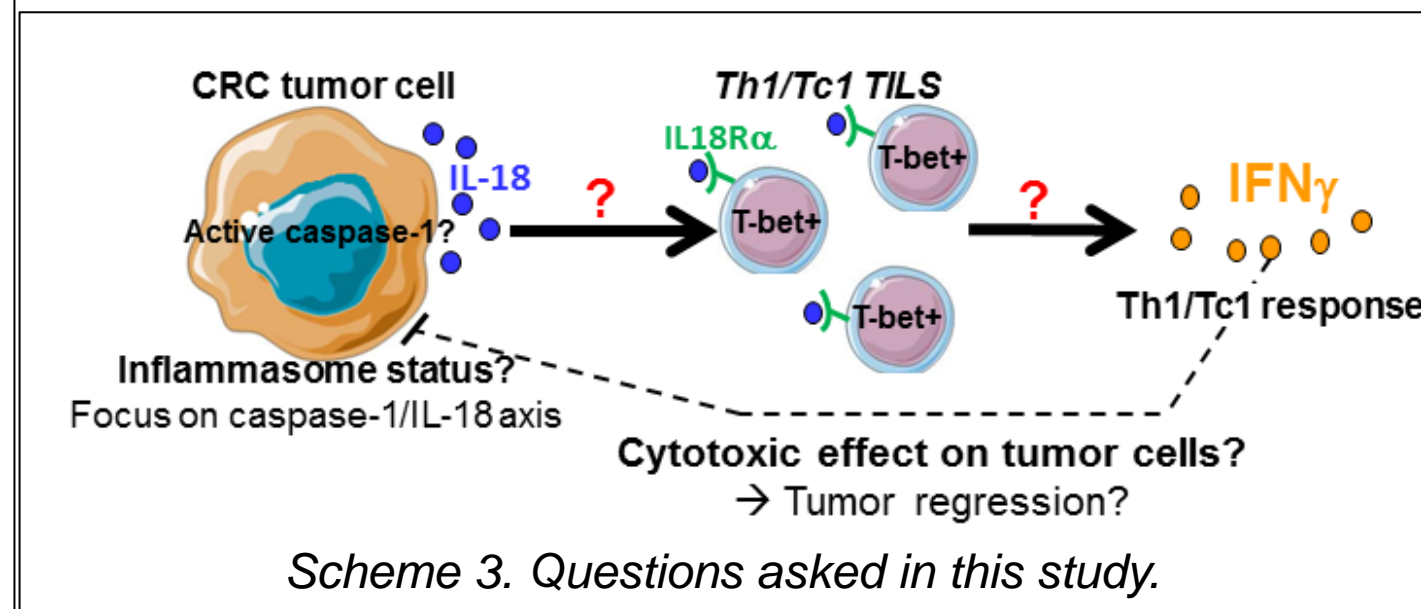
The **aims** of this work were to determine i) the inflammasome status in human CRC tumor cells and ii) its potential modulatory effect on the Th1/Tc1 response of TILs (scheme 3).



Kantono et Guo, Frontiers Immunol 2017
Scheme 2. The dynamic role of inflammasome in tumor development depending on the context.



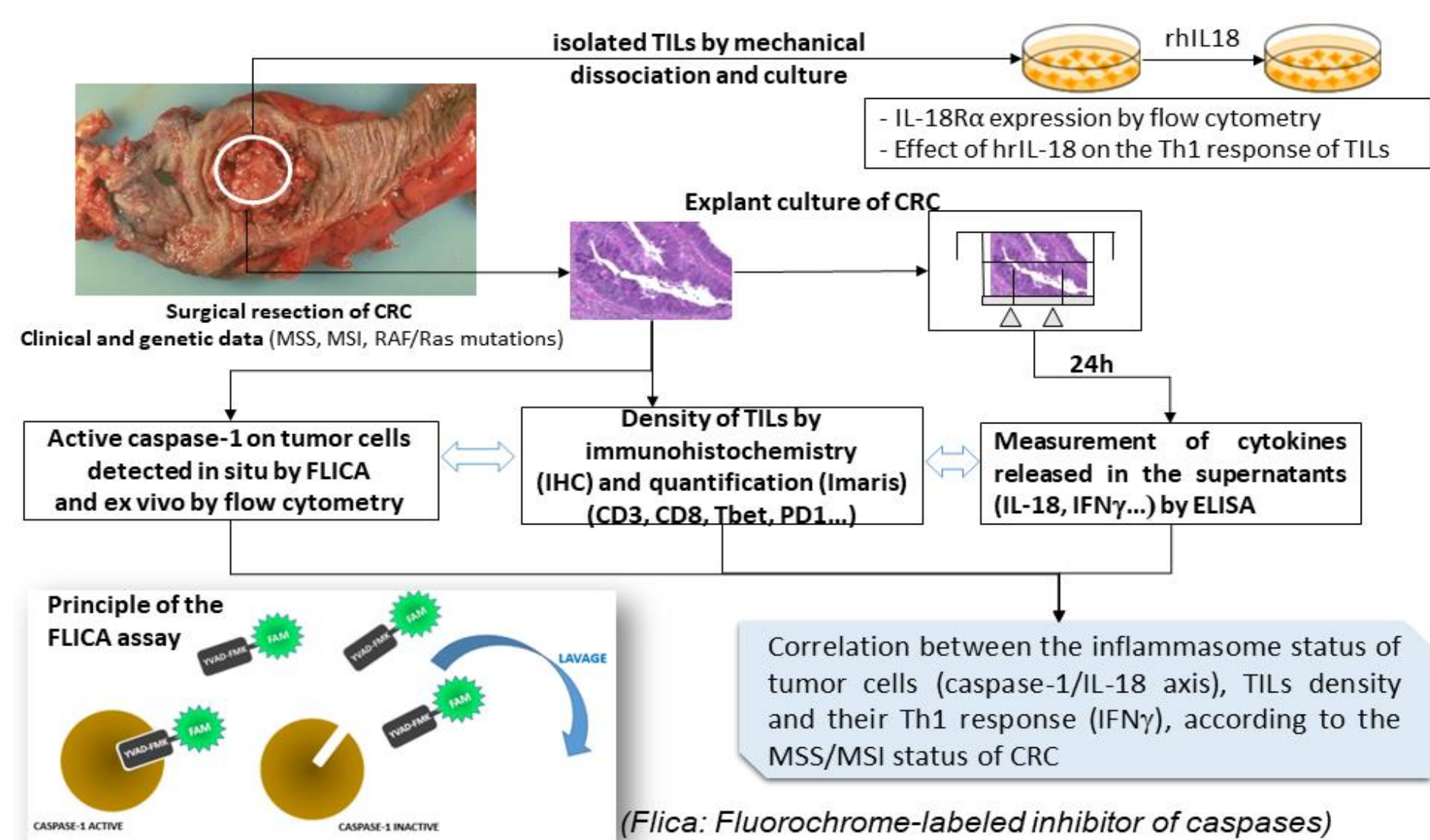
(Jarry et al, Gastroenterology, 2011)
Scheme 1. Normal intestinal epithelial cells contain a functional inflammasome.



Scheme 3. Questions asked in this study.

Patients and methods

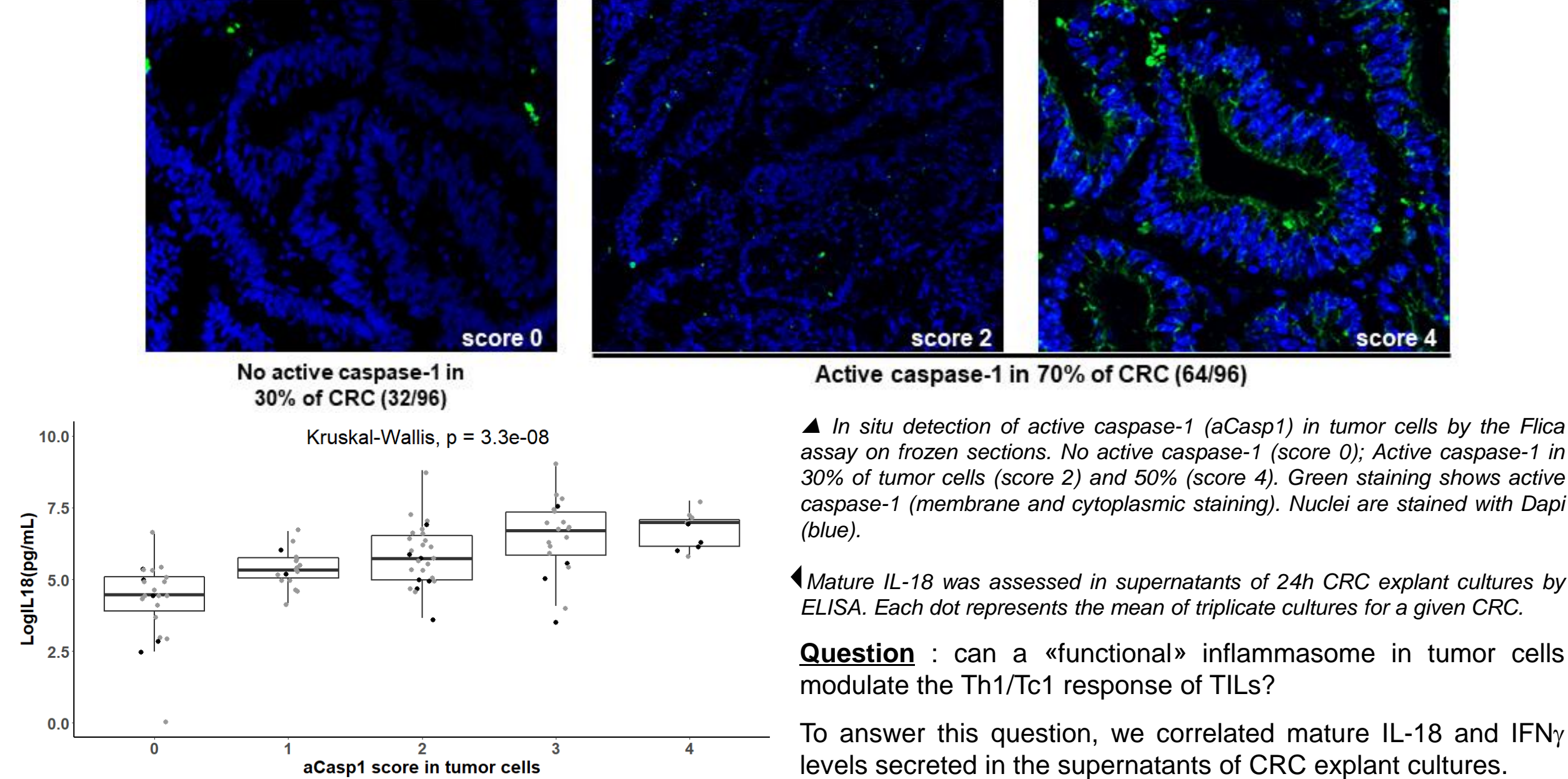
Prospective cohort of 96 CRC patients. Surgical resections of 74 microsatellite stable (MSS) and 22 microsatellite unstable (MSI) CRC. (2015-2019, in collaboration with the Pathology, Genetics, Digestive Surgery and Gastroenterology Depts, CHU Nantes, France). **Descriptive and functional studies using ex vivo explant cultures of CRC as well as isolated TILs maintained in culture.**



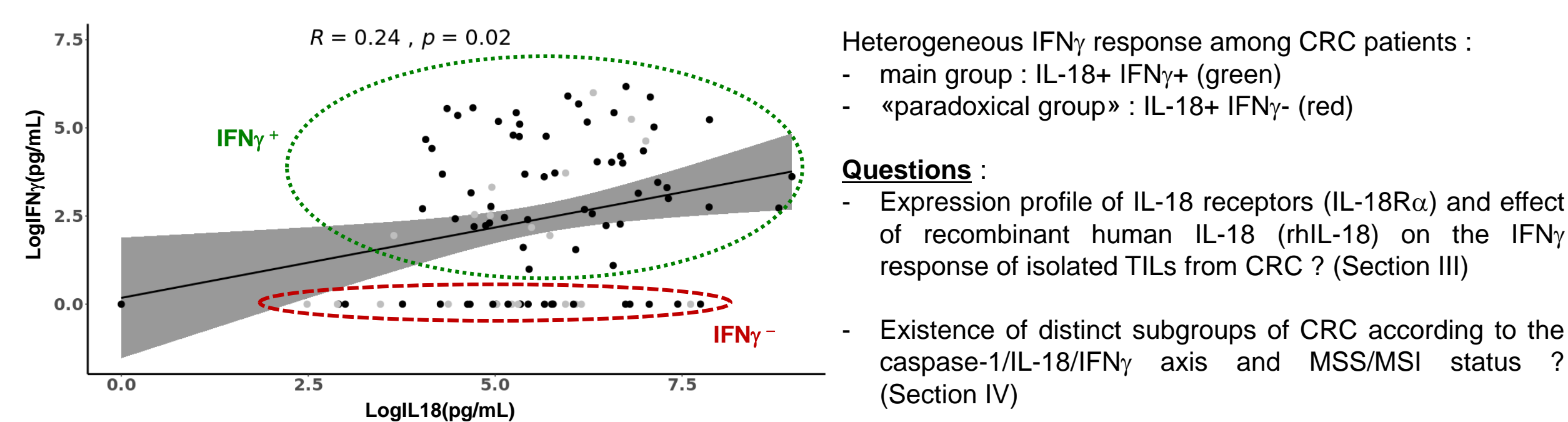
(Flica: Fluorochrome-labeled inhibitor of caspases)

Results

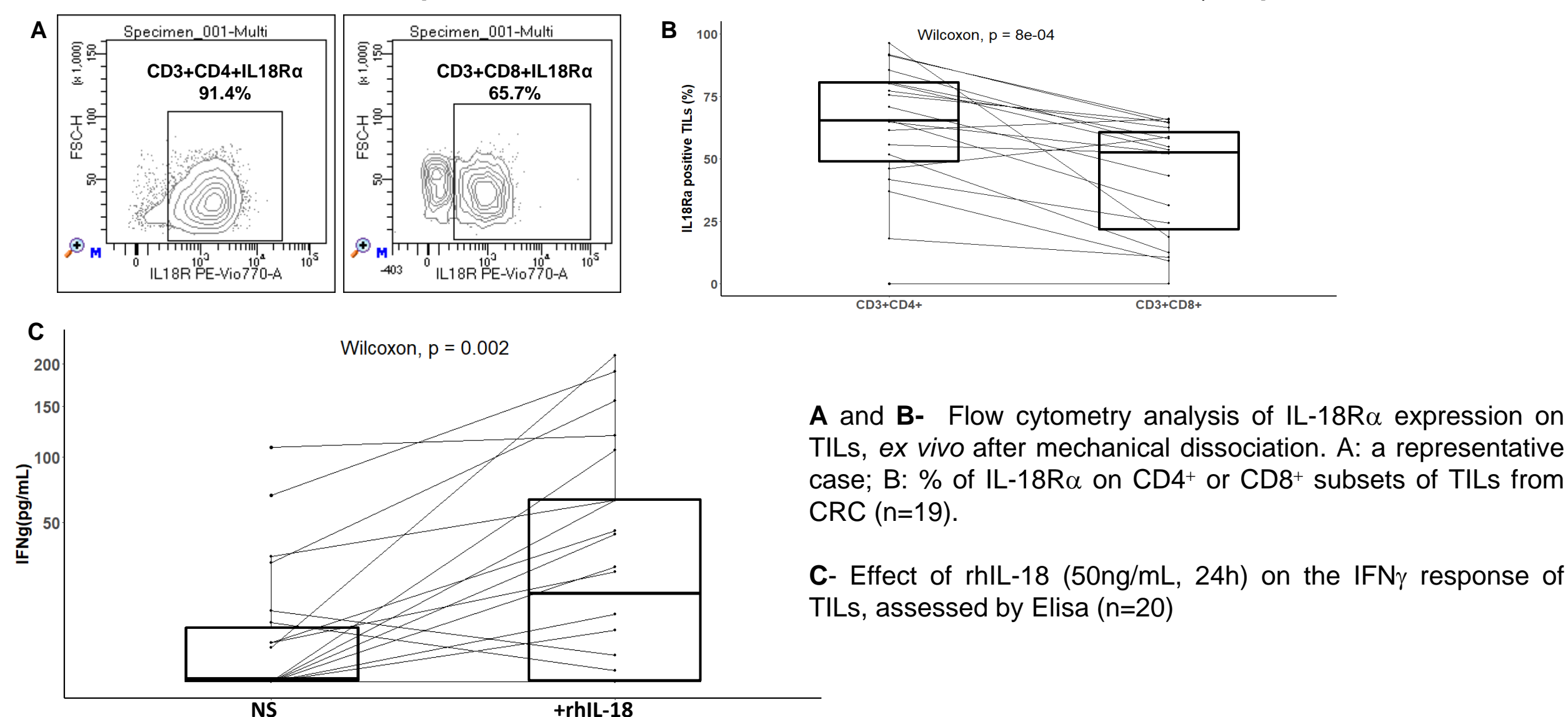
I. Active caspase-1 in tumor cells positively correlates with mature IL-18 levels secreted in explant cultures of CRC



II. Relationship between mature IL-18 and IFN γ released in ex vivo explant cultures of CRC



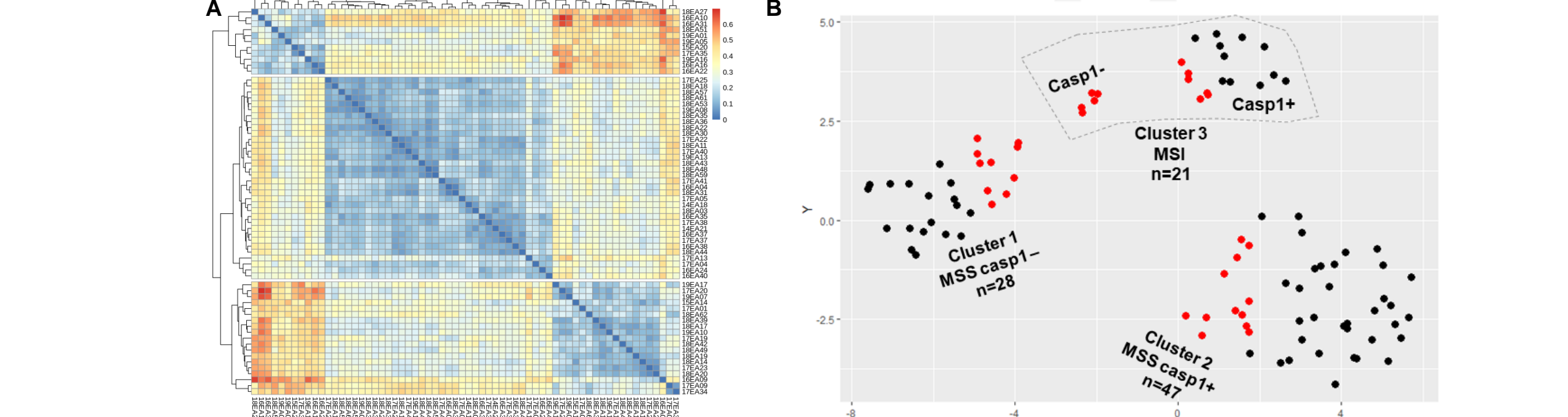
III. TILs isolated from CRC express IL-18Rα and rh IL-18 induces or enhances their IFN γ response



A and B- Flow cytometry analysis of IL-18R α expression on TILs, ex vivo after mechanical dissociation. A: a representative case; B: % of IL-18R α on CD4 $^{+}$ or CD8 $^{+}$ subsets of TILs from CRC (n=19).

C- Effect of rhIL-18 (50ng/mL, 24h) on the IFN γ response of TILs, assessed by Elisa (n=20)

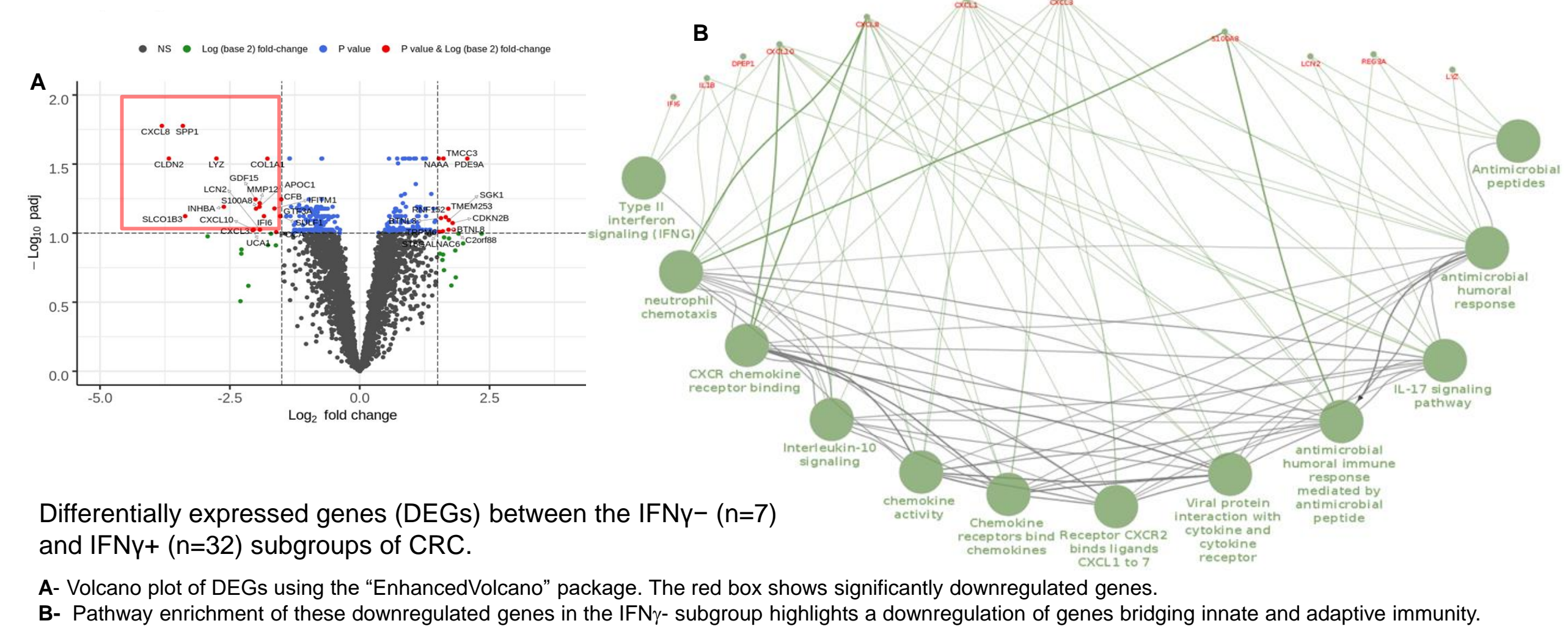
IV. Identification of subgroups of CRC according to the caspase-1/IL-18/TIL density/ IFN γ axis and microsatellite status



A non hierarchical cluster analysis led to the identification of 3 clusters of CRC according to the caspase-1 status in tumor cells: an expected, cluster of MSI CRC (cluster 3) and 2 clusters of MSS CRC, caspase1 $^{+}$ (cluster 2) or caspase1 $^{-}$ (cluster 1).
A- Heatmap on the dissimilarity matrix based on the Gower metric. **B-** Cluster visualization using a lower dimensional space with t-distributed stochastic neighborhood embedding (t-SNE). The **“paradoxical” IFN γ $^{-}$ CRC are distributed among these 3 clusters.**

Question: distinct transcriptomic profiles of IFN γ $^{-}$ versus IFN γ $^{+}$ CRC ?

IV. Transcriptomic profile of the IFN γ $^{-}$ vs IFN γ $^{+}$ subgroup of CRC



Differentially expressed genes (DEGs) between the IFN γ $^{-}$ (n=7) and IFN γ $^{+}$ (n=32) subgroups of CRC.

A- Volcano plot of DEGs using the “EnhancedVolcano” package. The red box shows significantly downregulated genes.
B- Pathway enrichment of these downregulated genes in the IFN γ $^{-}$ subgroup highlights a downregulation of genes bridging innate and adaptive immunity.

Conclusions

- This study delineates functional interactions between the inflammasome of tumor cells and TILs adaptive immunity and identifies subgroups of CRC according to the caspase-1/IL-18:TILs density/IFN γ axis.
- Our findings support the inflammasome of tumor cells as a potential target to strengthen the Th1/Tc1 immune response in CRC.

