NEW STRATEGY TO DISCRIMINATE PRO-TUMORIGENIC PATHWAYS

A research group from CIBER and Institut Hospital del Mar d'Investigacions Mèdiques (IMIM) has patented new IκBα mutants capable to predict the specific pathway altered in IκBα-deficient tumors.

The Need

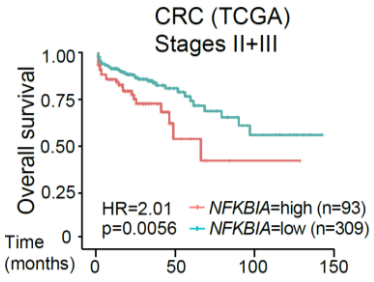
IκBα (nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor A) is a cellular protein which inhibits the NF-κB (nuclear factor-kappa B) transcription factor. Besides, it has been shown that IκBα can exert an alternatively function as a regulator of polycomb repression complex 2 (PRC2) activity.
There is an unmet medical need of finding reliable strategies for assessing whether a cancer type characterized by the inactivation of IκBα protein, which is a marker of poor prognosis, has been originated via activation of NF-κB or, alternatively, via PRC2 dysregulation.

The Solution

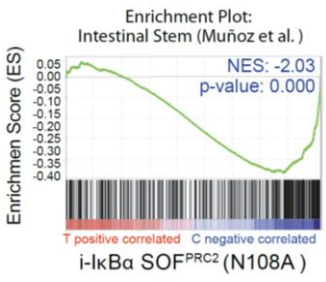
We have generated new separation-of-function IκBα mutants, which represent an innovative and unique tool for assessing whether a cancer type characterized by the inactivation of IκBα protein is originated by and depends on aberrant NF-κB activation or PRC2 miss-regulation. Identification of the driving force in specific IκBα-deficient cancer subtypes or individuals will have a clear impact in patient treatment management and will allow the design of specific inhibitors directed towards NF-κB or PRC2 pathways. Moreover, these mutants will allow setting-up medium or high-throughput platforms for the screen of clinically approved anti-cancer drugs.

Innovative Aspects

- Separation-of-function mutants has a clear impact in the treatment of patients carrying IκBα-deficient tumors (i.e., Hodgkin's lymphoma, squamous cell carcinoma, liver cancer or glioblastoma).
- They could also be used to better stratify patients either for diagnosis, therapy prescription and as inclusion criteria in clinical trials (A).
- The identification of the specific residues involved in the activation of the NF-κB pathway could be essential to develop specific inhibitors of NF-κB signaling in tumors, since all the existing compounds are very toxic in patients.



A. Representation of overall survival over time for CRC patients from the TCGA Portal, with high or low expression of *NFKBIA*.



B. GSEA of an intestinal stem cell (ISC) gene set associated to poor prognosis, from genes significantly repressed upon ectopic expression (16 hours) of i-IκBα SOF^{PRC2} (unchanged when expressing i-IκBα SOF $^{NF-κB}$).

Intellectual Property:

- Priority European patent application filed (March, 2nd 2022) suitable for international extension (PCT application)

Stage of Development:

Validated in "in vitro" experiments on transformed cells derived from colorectal cancer patients and with ongoing experiments in adult and pediatric glioblastoma.

Aims

Looking for a partner interested in a license and/or a collaboration agreement to develop and exploit this asset.

Contact details

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