Exosome based therapy in advanced breast and pancreatic cancer

LIVIA CARDOSO BUENO DE CAMARGO¹, FREDERIC GUADDACHI¹, DAVID BERGERAT², VERONIQUE PARIETTI², MARTINE CHOPIN³, PIERRE DE LA GRANGE⁴ AND SEBASTIEN JAULIAC⁴

(¹) Paris Diderot University, Saint-Louis Hospital, INSERM UMRS-976 (Paris, ile de France, France); (²) Inovarion SAS, (Paris, ile de France, France); (³) Paris Diderot University, Saint-Louis Hospital, Département d’Expérimentation Animale (Paris, ile de France, France); (⁴) Genosplice, Institut du Cerveau et de la Moelle épinière, ICM (Paris, ile de france, France)

Purpose: NFAT transcription factors are master regulators of tumor progression and metastases appearance in various cancer. Our team has shown that NFAT3, one of the 5 NFAT isotypes, depicts an anti-metastatic effect contradictory to NFAT1 and NFAT5 (1-5). In this context, recent studies suggest that exosomes, secreted by tumor cells, are fundamental in tumorigenesis. Therefore, we tried to develop a new way to inhibit tumor progression and ultimately metastases emergence by using exosomes produced by cells expressing the inhibitory factor NFAT3.

Experimental Design:

In vitro
Exosomes produced by low invasive breast cancer cells (T47D, MCF7) expressing endogenous NFAT3 were produced and tested for their capacity to inhibit in vitro breast cancer cell invasion of invasive breast cancer cells, glioblastoma and pancreatic cancer cells. Exosomes produced by low invasive breast cancer cells (T47D), where endogenous NFAT3 was downregulated by shRNA, were tested for their capacity to impede cell invasion. Exosomes produced by T47D or HEK293T cells over-expressing wild-type NFAT3 or a hyper-active mutant were tested for their capacity to impede cell invasion.

In vivo
In 2 mice models of cancer (breast and pancreas), the effect of the different exosomes tested in vitro were evaluated on tumor growth and metastases apparition.

Results: Our results in vitro demonstrate that exosomes produced by NFAT3-expressing breast cells are highly competent to blunt cell invasion in vitro of breast, melanoma, glioblastoma and pancreatic cancer cells. This inhibitory effect of the generated exosomes is incidental to NFAT3. Indeed, over-expressing NFAT3 in HEK293T cells is sufficient to transfer this inhibitory effect to the exosomes produced by HEK293T. Over-expressing an active mutant of NFAT3 in T47D of HEK23T cell is highly effective in increasing markedly the inhibitory capacity of the spawned exosomes.

Our results in vivo extend our in vitro data and revealed that exosomes produced from NFAT3-expressing cells are robustly potent in impeding tumor growth and metastases apparition.

Conclusion:
We have identified a new potential therapeutical approach to treat advance breast and pancreatic cancer based on exosomes produced by NFAT3-expressing cells

References:
3- Fougère M et al. Oncogene. 2010 ;29(15):2292-301
Patent WO2017167788