Pre-clinical studies on the therapeutic potential of all-trans-retinoic acid in the personalized treatment of gastric cancer.

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**Overview**

- All-trans retinoic acid (ATRA), the active metabolite of vitamin A, is the first example of targeted therapeutics and it is successfully used in the treatment of acute promyelocytic leukaemia (APL)\(^1\). In combination with chemotherapy or arsenic trioxide, ATRA induces complete remission in >90% of APL patients and remission is maintained for at least 5-7 years in the majority of cases. These exceptional clinical results have raised interest in the potential of ATRA as an anti-tumour agent also for solid tumours, with particular reference to diseases which are devoid of viable therapeutic options, like gastric cancer (GC).
- Gastric cancer (GC) is a heterogeneous type of tumour. Hence, personalized use of ATRA in the clinics calls for the identification of the subtypes responsive to ATRA-based therapeutic protocols, and the development of a diagnostic tool capable of predicting ATRA-sensitivity.

**Methods**

A panel of 15 gastric cell line (Fig. 2A) was used for the completion of the aims. Cell lines was exposed to increasing concentrations of ATRA (10 nM-10 µM) for 6 days. Growth inhibition was determined with the sulforhodamine assay. A multi-parametric cell-inhibition score (“ATRA-score”) was applied to rank the cell lines in a continuous manner according to ATRA sensitivity. In order to perform out an RNA-Seq (Fig. 2B), the RNA was processed with the TruSeq stranded RNA library preparation kit (Illumina) and sequenced on the Illumina NextSeq500 apparatus with paired-end, 121-base pair long reads. Analysis of the high-throughput data generated was performed with the computational methodologies using the R Statistical environment (Fig. 2C).

**Results**

Using a PCA representation (Fig. 3A) it was possible to cluster the gastric cancer cell line through RNA-Sequencing data. Principal component analysis helps to describe the differences among the samples, and it is made by taking into account the first 2000 genes that express the largest variance. The results show the formation of 2 distinct clusters. This may suggest a dual transcriptional point of view was obtained. In order to validate these results, it may be useful to discriminate transcriptional differences between the 2 groups. In this study, several works where subdivisions have been made on the basis of the transcriptomic profile of gastric carcinomas. An optimal idea would be to investigate the most appropriate method, and to identify a genomic signature explaining the molecular differences. Moreover, the identification of a predictive model of ATRA-sensitivity and the application of the latter in tissue cultures of primary GC tumors patients is necessary.

**Conclusions**

- Based on these results, a finer subdivision from transcriptional point of view was obtained. In order to validate these results, it may be useful to discriminate transcriptional differences between the 2 groups. In literature, there are several works where subdivisions have been made on the basis of the transcriptomic profile of gastric carcinomas.
- An optimal idea would be to investigate the most appropriate method, and to identify a genomic signature explaining the molecular differences. Moreover, the identification of a predictive model of ATRA-sensitivity and the application of the latter in tissue cultures of primary GC tumors patients is necessary.

**References**