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Version: Poster
Pre-Clinical Studies on the Therapeutic Potential of All-Trans-Retinoic Acid in the Personalized Treatment of Gastric Cancer

Luca Guarrera1, Mami Kurosaki2, Maurizio Gianni2, Gabriela Paroni2, Maria Chiara Barbera2, Laura Di Rito2, Ilaria Craparotta2, Marco Bolis2,3, Mineko Terao4 and Enrico Garattini2.

1Computational Oncology Unit, Department of Oncology, “Mario Negri Institute for Pharmacological Research IRCCS”, Milan, Italy.
2Laboratory of Molecular Biology, “Mario Negri Institute for Pharmacological Research IRCCS”, Milan, Italy.
3Institute of Oncology Research, Bellinzona, Switzerland. 4Università Della Svizzera Italiana, Lugano, Switzerland.

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 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 profile that divides the GC cell lines into two subtypes. The second step of RNA-Seq Data Samples processing consisted of the evaluation of the differential expression between the experimental groups, represented respectively by the ATRA treatment and DMSO treatment, and the corresponding “Gene Set Enrichment Analysis” (Fig. 3B).

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 carcinoma.
- 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