biology and life sciences forum

MDPI

Abstract

Modulation of Retinoic Acid Receptor Signaling Pathway via All-Trans Retinoic Acid in Merkel Cell Carcinoma Cells †

John Charles Rotondo [1,*], Chiara Mazziotta [1], Giampaolo Morciano [1], Christian Felice Cervellera [1], Giada Badiale [1], Giulia Tonnini [1], Giulia Di Mauro [1], Paolo Pinton [1], Antoine Touzé [2], Pauline Gaboriaud [2], Mauro Tognon [1] and Fernanda Martini [1]

[1] Department of Medical Sciences, University of Ferrara, 44121 Ferrara, Italy; mzzchr@unife.it (C.M.); mrcgpl@unife.it (G.M.); christianfelice.cervellera@unife.it (C.F.C.); giada.badiale@unife.it (G.B.); giulia.tonnini@edu.unife.it (G.T.); giulia.dimauro@unife.it (G.D.M.); paolo.pinton@unife.it (P.P.); mauro.tognon@unife.it (M.T.); fernanda.martini@unife.it (F.M.)

[2] ISP "Biologie des infections à polyomavirus" Team, UMR INRAE 1282, University of Tours, 37200 Tours, France; antoine.touze@univ-tours.fr (A.T.); pauline.gaboriaud@univ-tours.fr (P.G.)

* Correspondence: rtnjnc@unife.it; Tel.: +39-0532-455-536

† Presented at Cells, Cells and Nothing but Cells: Discoveries, Challenges and Directions, 6–8 March 2023; Available online: https://cells2023.sciforum.net/.

Abstract: The biological activity of retinoic acid or all-trans retinoic acid (ATRA) is mediated by retinoic receptors, which are ligand-dependent transcription factors that activate genes crucial for cell differentiation. Dysregulations of retinoic receptor signaling pathway led to carcinogenesis. A strong in vitro/in vivo antitumor activity of ATRA by modulating the retinoic pathway has been proved in carcinoma of different histotypes. However, the effect of this molecule in Merkel cell carcinoma (MCC), a rare but aggressive skin neoplasm of viral origin in 80% of cases, is unknown. Herein, we investigated the antineoplastic effect of ATRA in Merkel cell polyomavirus (MCPyV)-positive/-negative MCC cells and in human fibroblasts as controls. The antineoplastic effect of ATRA was evaluated at day 3 of treatment by testing MCC cell proliferation, migration, and clonogenicity. Apoptosis/cell death and cell cycle were evaluated via Annexin-V/propidium iodide (P.I.) and TALI assays, respectively. Apoptotic and retinoic pathways were evaluated by RT^2 Profiler PCR mRNA array, which allows the analysis of pro/anti-apoptotic and retinoic pathway genes (84 + 84 genes), as well as by Western blot (WB) analysis. ATRA treatment led to a strong reduction in MCC cell proliferation, migration and clonogenicity, while inducing cell cycle arrest and promoting apoptosis/death in MCC cells, with a more pronounced effect in MCPyV-positive MCC cells. A significant overexpression of various pro-apoptotic markers in ATRA-treated MCC cells compared to untreated cells was determined by gene expression array and WB analyses. No phenotypic and molecular effects were identified in ATRA-treated fibroblast control cells. Upon ATRA treatments in MCC cells, numerous retinoic signaling genes, such as *BMP2*, *FOXA1*, *MAFB*, *RBP4*, *OLIG2*, *UCP1* were found to be differentially expressed compared to untreated cells. Our in vitro data indicate that ATRA is effective in reducing MCC cell growth while presenting strong pro-apoptotic effects and favoring cell cycle arrest/death via retinoic receptor signaling pathway regulation.

Keywords: Merkel cell carcinoma; Merkel cell polyomavirus; all-trans retinoic acid

check for updates

Citation: Rotondo, J.C.; Mazziotta, C.; Morciano, G.; Cervellera, C.F.; Badiale, G.; Tonnini, G.; Di Mauro, G.; Pinton, P.; Touzé, A.; Gaboriaud, P.; et al. Modulation of Retinoic Acid Receptor Signaling Pathway via All-Trans Retinoic Acid in Merkel Cell Carcinoma Cells. *Biol. Life Sci. Forum* **2023**, *21*, 27. https://doi.org/10.3390/blsf2023021027

Academic Editor: Alexander E. Kalyuzhny

Published: 24 March 2023

Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

Author Contributions: Conceptualization, J.C.R. and F.M.; methodology, C.M.; software, G.M.; validation, C.F.C., G.B. and G.T.; formal analysis, C.M.; investigation, G.D.M.; resources, P.P., A.T., P.G.; data curation, C.M.; writing—original draft preparation, J.C.R.; writing—review and editing, J.C.R.; supervision, A.T. and M.T.; project administration, F.M. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported, in part, by grants MFAG 21956 (to J.C.R.), IG 21617 (to M.T.) from the Associazione Italiana per la Ricerca sul Cancro (AIRC), Milan, Italy, and University of Ferrara,

FAR grants 2021 (F.M. and M.T.). J.C.R. was supported by Umberto Veronesi Foundation. C.M. was supported by a AIRC fellowship for Italy (ID: 26829) and by "Bando Giovani anno 2022 per progetti di ricerca finanziati con il contributo 5 × 1000 anno 2020".

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.