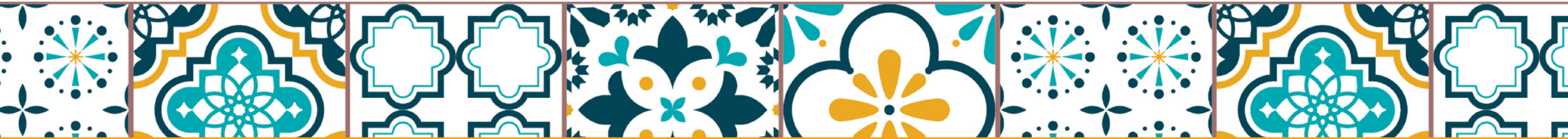
Check for updates

Molecular Oncology

ISSN 1574-7891
Volume 19 Supplement 1
June 2025

A journal for discovery-driven translational cancer research



2025.eacr.org

WILEY

www.moloncol.org

ribonucleotide reductase (RNR), MK1775 as a Wee1 inhibitor, and siRNA targeting Wee1.

Result and discussion

Metabolomic analysis revealed that pyrimidine and purine nucleotides were among the most differentially regulated metabolites, decreasing in brequinar- and AICAr-treated samples while increasing in AraC-treated samples. When cells were cultured in αMEM supplemented with 10 mg/ml of both rNs and dNs, the effects of all tested agents on proliferation, differentiation, and cell cycle arrest were completely abolished. All agents increased RRM2 expression, suggesting a role for RNR in differentiation. Inhibition of Wee1 kinase with MK1775 blocked RRM2 upregulation and AML differentiation without preventing S-phase arrest. Similar effects on differentiation and the cell cycle were observed in cells treated with COH29, a recently described RNR inhibitor. However, HU, a well-known RNR inhibitor, failed to prevent differentiation. Experiments are underway to further investigate the role of RNR in cells with downregulated expression.

Conclusion

Our findings suggest that ribonucleotide metabolism regulates AML differentiation, with Wee1 and RNR activation occurring downstream of replication stress.

EACR25-1356
CFTR modulator drugs can reduce the invasive properties of colorectal cancer cells

L. Vicente[1,2], P. Barros[1,2], V. Gonçalves[1,2], P. Oliveira[3], P. Jordan[1,2], P. Matos[1,2]

[1]Instituto Nacional de Saúde Doutor Ricardo Jorge (INSA), Departamento de Genética Humana, 1649-016 Lisboa, Portugal

[2]BioISI – Instituto de Biossistemas e Ciências Integrativas, Faculdade de Ciências, Universidade de Lisboa, 1749-016 Lisboa, Portugal

[3]Centre for Research and Technology of Agro Environmental and Biological Sciences (CITAB), Inov4Agro, University of Trás-os-Montes and Alto Douro (UTAD), Vila Real, Portugal

Introduction

Colorectal cancer (CRC) remains a leading cause of cancer-related mortality, driven by complex genetic, epigenetic, and microenvironmental factors. Recent findings implicate the cystic fibrosis transmembrane conductance regulator (CFTR) ion channel in CRC progression, as CFTR levels are notably reduced in sporadic CRCs, particularly in advanced and metastatic tumors, correlating with poorer patient outcomes. Additionally, cystic fibrosis (CF) patients, who carry CFTR mutations, have a 6-fold increased risk of early-onset CRC. Given recent advances in small-molecule modulators that restore CFTR function in CF patients, this study explored the potential of repositioning these modulators to address CFTR downregulation in sporadic CRC.

Material and method

Using a panel of CRC cell lines, we investigated whether CFTR modulators can increase CFTR functional expression in cells with various genetic backgrounds and whether such improvements could reduce their oncogenic properties.

Result and discussion

Our data show that treatment with the CFTR folding correctors VX-661 and VX-445 led to a significant, approximately three-fold increase in CFTR abundance in CRC cells expressing reduced but detectable levels of the channel. Additionally, these treatments significantly reduced the migratory and invasive behavior of Caco-2 and DLD-1 cells, particularly when combined with the CFTR potentiator VX-770.

Conclusion

Our findings suggest that CFTR modulators may hinder the oncogenic properties of CRC cells. Further in vivo studies are necessary to fully assess their potential benefits for repositioning as a CRC treatment.

EACR25-1362
CDK6 inhibition coupled with Vitamin D receptor activation synergistically promotes AML differentiation and cell death

A. Boudet[1,2,3], L. Brault[1,4,3], C. Savey[1,4,3], A. Izac-Imbert[1,4,3], J. Vernerey[1,5,6], P. Kousteridou[1,4,3], S. Letard[1,4,3], S. Lopez[1,4,3], P. De Sepulveda[1,4,3]

[1]CRCM – Cancer Research Center of Marseille, Marseille, France

[2]INSERM U1068, Marseille, France

[3]CNRS UMR7258, Marseille, France

[4]INSERM U1068, Marseille, France

[5]INSERM U1068, Marseille, Costa Rica

[6]CNRS UMR7258, Marseille, Cuba

Introduction

Acute Myeloid Leukemia (AML), the most prevalent acute leukemia in adults, is a devastating cancer, with a 5-year survival rate of 35-40% in patients under 60 years and only 5–15% in older patients. AML is a heterogeneous disease caused by acquired genetic modifications in stem and progenitor cells. Leukemic cells fail to differentiate and invade the bone marrow, interfering with the renewal of mature blood cells. In this pathology, relapse and resistance to therapies are the primary causes of mortality. Many patients are not eligible for conventional intensive chemotherapy. The standard treatment for these unfit patients is a combination of venetoclax (a BCL2 inhibitor) in association with azacytidine (a DNMTs inhibitor). However, at least 60% of those patient will relapse. Therefore novel treatments remain critically needed to eradicate AML cells, including leukemic stem cells.

Material and method

AML cell lines and primary samples were treated with a combination of CDK6 inhibitors and VDR agonists. Differentiation and cell death were assessed via flow cytometry, caspase activity assays, and RNA sequencing. Clonogenic potential was evaluated using colony-forming unit assays. To better understand our transcript-omic results, chromatin accessibility was analyzed through ATAC-seq. Proliferation and cell death assays were conducted to assess venetoclax sensitivity in resistant models.

Result and discussion

© 2025 The Authors. Molecular Oncology is published by John Wiley & Sons Ltd on behalf of Federation of European Biochemical Societies

18780261, 2025, S1, Downloaded from https://febs.onlinelibrary.wiley.com/doi/10.1002/1878-0261.70070 by Cochrane Portugal, Wiley Online Library on [17/07/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License