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ARID1A mutations in colorectal cancer: Biological and therapeutic implications

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Introduction: The AT-interacting domain-rich protein 1A (*ARID1A*) gene undergoes mutations in approximately 10% of human colorectal cancer (CRC). The loss of function (LOF) associated with these mutations is intricately linked to the onset and advancement of CRC, and it serves as a prognostic indicator for unfavorable outcomes in CRC patients. Despite this, the exploration of the clinical implications and applications of *ARID1A* mutations remains relatively constrained.
Objectives: To delve deeper into the connection between *ARID1A* mutations and CRC, as well as to unravel the associated signaling pathways. This investigation seeks to identify and screen clinical drugs that specifically target *ARID1A* mutations.
Methods: In this investigation, the Cre-loxP system was employed to create *Arid1a* mutant mouse models. We produced CRC organoids, namely *Arid1a*$^{flox/flox}$;*Apc*$^{flox/flox}$;*Kras*$^{ki/wt}$;*Trp53*$^{flox/flox}$ (ArAKPf) and *Apc*$^{flox/flox}$;*Kras*$^{ki/wt}$;*Trp53*$^{flox/flox}$ (AKPf), as well as human CRC cell line models featuring ARID1A knockout (KO) through CRISPR technology. These models were subsequently utilized in functional experiments.
Results: In comparison to the AKPf cell line, the ArAKPf cell line exhibited a significant augmentation in colony formation. This proliferative enhancement was substantiated by the cell counting kit-8 (CCK-8) assay, affirming heightened proliferative capabilities in the ArAKPf and HCT116 *ARID1A*^{KO} cell line. Wound healing assays manifested a substantial increase in migratory distance for the *ARID1A* mutant cell line, and Boyden chamber assays unveiled a pronounced escalation in both migratory and invasive capacities of the ArAKPf and HCT116 *ARID1A*^{KO} cell line. Subsequent bioinformatics analyses implicated Arid1a in the modulation of molecules integral to the phosphatidylinositol 3-kinase (PI3K)/AKT signaling pathway. This proposition was validated through quantitative reverse transcription PCR (RT-qPCR) assessments. Furthermore, drug screening delineated an extensive resistance profile in *Arid1a*-mutated mouse CRC cells. However, these cells demonstrated susceptibility to B-cell lymphoma 2 (BCL-2) inhibitors.
Conclusion: The findings suggest that *ARID1A* mutation confers heightened proliferative, migratory, and invasive capacities upon mouse and human CRC cells, concurrently resulting in a broad spectrum of drug resistance. Notably, BCL-2 inhibitors emerge as potential therapeutic alternatives in addressing these phenotypic changes.