Majumder et al. (2017) Can J Biotech, Volume 1, Special Issue (Supplement), Page 252
https://doi.org/10.24870/cjb.2017-a236

Canadian Journal of Biotechnology

ISSN 2560-8304

Poster Presentation **OPEN ACCESS**

Category: Clinical Genomics

A neoepitope derived from a novel germline *Adenomatous polyposis coli* (APC) gene mutation in Familial Adenomatous Polyposis (FAP) shows selective immunogenicity

Snigdha Majumder[1], Rakshit Shah[2], Jisha Elias[1,2], Yogesh Mistry[2], Coral Karunakaran[1], Priyanka Shah[1], Anand Kumar Maurya[1], Bharti Mittal[1], Jason K. D'Silva[1], Lakshmi Mahadevan[1], Rekha Sathian[1], Ravi Gupta[1], Amitabha Chaudhuri[1,3] and Arati Khanna-Gupta[1*]

[1]MedGenome Labs Pvt. Ltd., Bangalore, INDIA

[2]KCHRC, Muni Seva Ashram, Goraj, Gujarat, INDIA

[3]MedGenome Inc., Foster City, CA, USA

*Corresponding author: arati.g@medgenome.com

Abstract

Familial Adenomatous Polyposis (FAP) is characterized by the manifestation of adenomatous polyps in the colon and rectum at an early age (mean age of 16), which if left untreated, leads to aggressive and fatal tumors by the age of 40 years. FAP is caused by autosomal dominant inheritance of germ line mutations in the *Adenomatous polyposis coli* (*APC*) gene, a well characterized tumor suppressor gene. Over fifty percent of FAP affected individuals with germline mutations eventually develop colon cancer and therapeutic intervention to prevent cancer progression remains a major unmet medical need. In the last five years, therapies aimed at restoring or enhancing the host's immune response to treat cancers has gained momentum. Cancer immunotherapy triggers a patient's immune system to destroy tumor cells (apoptosis) by recognizing tumor-derived neoantigens, presented on the tumor cell surface as peptides bound to class I and II major histocompatibility complex (MHC). Our approach in this study was to determine if FAP could be targeted by immunotherapeutic approaches to reduce polyp numbers, thereby limiting the risk of progression to colorectal cancer.

In this study, we identified a novel germline mutation in the *APC* gene in 10/26 members of a FAP-affected family. To find out if peptides derived from the novel APC mutation could induce a cytotoxic T cell response, peptides harboring the variant amino acids were first interrogated *in silico* for their immunogenicity using a proprietary neoepitope prioritization pipeline, OncoPept*VAC*. A single 9-mer peptide was predicted to be immunogenic. Remarkably, $CD8^+$ T cells isolated from either a FAP^+/ APC^{mut} individual, or from a FAP^-/ APC^{mut} individual, failed to respond to the peptide, whereas those from either an unaffected family member (FAP^-/ APC^{wt}) or from healthy unrelated donors with same HLA type, showed a robust response. We conclude that $CD8^+$ T cells from affected individuals carrying this germline APC mutation have been tolerized against the mutation. Additionally, *in silico* analyses showed that of the 996 previously reported *APC* gene mutations in FAP, 42% are potentially immunogenic. These immunogenic mutations could provide novel opportunities to treat FAP patients and to delay their progression to colorectal cancer.

Citation: Majumder, S., Shah, R., Elias, J., Mistry, Y., Karunakaran, C., Shah, P., Maurya, A.K., Mittal, B., D'Silva, J.K., Mahadevan, L., Sathian, R., Gupta, R., Chaudhuri, A. and Khanna-Gupta, A. A neoepitope derived from a novel germline *Adenomatous polyposis coli* (APC) gene mutation in Familial Adenomatous Polyposis (FAP) shows selective immunogenicity [Abstract]. In: Abstracts of the NGBT conference; Oct 02-04, 2017; Bhubaneswar, Odisha, India: Can J biotech, Volume 1, Special Issue (Supplement), Page 252. https://doi.org/10.24870/cjb.2017-a236