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**Gut microbial-derived N-acetylmuramic acid alleviates colorectal cancer via the AKT1 pathway**

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Evidence has started emerging that metabolites of the intestinal microbiota influence colorectal cancer (CRC) development. Peptidoglycan fragments (PGFs), as one such group of these, whilst previously shown to contribute to maintenance of intestinal homeostasis, make an as yet unclear contribution to CRC pathogenesis. This work looked to explore the role of PGFs in development of intestinal neoplasia.

This was evaluated through a suite of studies. The relative abundance of genes responsible for peptidoglycan synthases/hydrolases was assessed by metagenomic analysis. Using targeted mass spectrometry, quantification of certain PGFs (stool and serum) of CRC patients was performed. Direct effects of PGFs were examined in organoids derived from CRC patients, as well as mouse models. Finally, a combination of proteome microarray, transcriptome sequencing and rescue assays were used to examine their downstream molecular targets.

In terms of findings, among 1121 CRC cases, a significant reduction in relative abundance of peptidoglycan synthase genes was demonstrated. Mass spectrometry data showed patients with CRC had significantly lower levels of a specific PGF – N-acetylmuramic acid (NAM) – which decreased as tumours progressed. In patient-derived CRC organoids – NAM – was also demonstrated to inhibit growth proportionate to its concentration, and inhibited tumour development in multiple mouse models, in addition. Finally, subsequent studies assessing downstream effects, suggested inhibition by NAM of AKT1 (RAC(Rho family)-alpha serine/threonine-protein kinase) activation (through direct binding thus blocking phosphorylation) to represent a potential mechanism of action.

In conclusion, in addition to their established role in intestinal homeostasis, this group has generated novel evidence of the possible role of PGFs in intestinal tumorigenesis, with an apparent paucity of such molecules (specifically NAM) in the setting of CRC, and a potential inhibitory effect of them in a human organoid/mouse setting, possibly effected via the AKT1 signalling pathway. PGFs (NAM, in particular) may therefore represent an exciting new potential biomarker in CRC management.