



Signals derived from the commensal microbiota to promote intestinal tumor development

Swapna Chaudhuri

Department of Laboratory Medicine, School of Tropical Medicine, West Bengal, India

Correspondence to: Swapna Chaudhuri. Department of Laboratory Medicine, School of Tropical Medicine, 108, C.R.Avenue, Kolkata 700073, West Bengal, India. Email: swapna.chaudhuri@gmail.com.

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Chronic inflammation can stimulate carcinogenesis in an individual, as is evident by the association between chronic inflammatory bowel diseases and the increased risk of colon carcinoma. Various factors, like bacterial, viral, and parasitic infections, chemical irritants, and nondigestible particles can lead to chronic inflammation. Carcinogenesis is directly related to the time period of inflammation and Chronic Inflammation. Though many common molecular mediators are generated in both acute and chronic inflammation, acute inflammation, like in response to a transient infection, is not regarded as a risk factor for the development of cancer (1). The inflammatory response is characterized by coordinate activation of various signalling pathways that regulate expression of both pro- and anti-inflammatory mediators in resident tissue cells and leukocytes recruited from the blood (2). In the intestinal epithelium tumor development is stated to be promoted by the signalling pathways of STAT3 and (NF)- κ B. Signal transducer and activator of transcription (STAT) proteins play a central role in determining whether in the tumour microenvironment immune responses promote or inhibit cancer. Tumour cell proliferation, survival and invasion increase by continual activated STAT3 and STAT5 but they suppress anti-tumour immunity. Tumour-promoting inflammation is also mediated by persistent activation of STAT3. STAT3 promotes pro-oncogenic inflammatory pathways, like nuclear factor- κ B (NF- κ B) and interleukin-6 (IL-6)-GP130-Janus kinase (JAK) pathways, and opposes STAT1- and NF- κ B-mediated T helper 1 anti-tumour immune responses (3).

The article entitled “Epithelial calcineurin controls microbiota-dependent intestinal tumor development” by Kenneth Peuker *et al.* was an Advance online publication

in *Nature Medicine* (published online 4 April 2016; doi:10.1038/nm.4072). They report that ‘Intestinal inflammation as observed in inflammatory bowel disease (IBD) is a risk factor for the development of colorectal cancer (CRC)’. Inflammation damages the mucosal lining of the intestine and can alter the composition of the gut microbiome, enabling the interaction of gut microbes with the epithelia (4).

Peuker *et al.* reported that microbiota stimulated the proliferation of CRC-associated stem cells through the activation of calcineurin, which is a phosphatase activating transcription factors in the NFAT family. Interestingly the authors observed that *in vivo* inhibition of calcineurin leads to an increase in the incidence of solid cancers including CRC but *in vitro* inhibition of calcineurin retards CRC cell growth, correlating that through the regulation of cancer stem cell function in mice epithelial calcineurin promotes intestinal tumor development. Moreover, somatic mutations that have been identified in human CRC are associated with constitutive activation of calcineurin, whereas nuclear translocation of NFAT is associated with increased death from CRC. The growth of human CRC cells *in vitro* is dependent on calcineurin and NFATc3. To search whether NFATc3 promotes tumor development downstream of calcineurin, it was found that constitutive tumor-associated activation of NFATc3 occurs in the presence of functional calcineurin. To further address this question, the authors searched whether NFATc3 activation and nuclear translocation in human CRC are associated with cancer-related death in individuals with CRC. These results pointed to the fact that the activation and nuclear translocation of NFATc3 is associated with increased death of individuals from CRC. Studies with NFATc1

binding to *Lgr5* and *Dclk1* in hair follicle stem cells questioned whether alterations in direct NFAT-dependent transcription contribute to the decreased expression of stem cell-associated genes. Experimental data suggested that alterations in direct NFAT-dependent transcription, as well as a loss of tumor stem cells, contribute to decreased expression of stem cell-associated genes (5).

TLR-induced Myd88 signaling in the nonhematopoietic compartment, and specifically in the IECs, regulates tumor growth through control of epithelial proliferation and apoptosis (6,7). Microbes that trigger an innate immune response through the activation of Toll-like receptors (TLRs) and CRC cells are TLR2 and TLR4 positive. TLR agonists have been shown to activate calcineurin and NFAT in dendritic cells. Experiments pointed that TLR stimulation promotes store-operated calcium entry, nuclear NFAT translocation and NFAT-dependent transcription in CRC cells (5). The results indicate that tumor-promoting effects of epithelial calcineurin extend to the colon and to colitis-associated CRC. This suggests that intestinal tumor initiation and growth in mice is supported by epithelial calcineurin. Epithelial proliferation and apoptosis inhibition causes intestinal tumor development supported by calcineurin. One isoform of the endogenous calcineurin regulator, Down syndrome candidate region-1 (DSCR1. Ex4), suppresses calcineurin-NFAT signaling blocking endothelial proliferation. But, overexpression of DSCR1 isoform (DSCR1.Ex1) may promote angiogenesis (8). Ryeom *et al.*, in 2008 reported that targeted deletion of both isoforms causes hyperactivated calcineurin and precocious endothelial apoptosis, inhibiting angiogenic vasculature and suppressing tumorigenesis. Calcineurin inhibitor cyclosporin A rescues this endothelial defect in DSCR1 (-/-) mice, restoring tumor growth. Also, it was reported that patients treated with cyclosporin A and FK506 to prevent graft rejection dramatically increases the risk of cutaneous squamous cell carcinoma (9). CnA α , an isoform of calcineurin, was significantly over expressed in lung cancer tissues with bone metastasis as compared to tumors with non-bone metastases. Calcineurin promotes proliferation, migration, and invasion of small cell lung cancer (10).

Bacterial translocation into intestinal adenomas, as well as an increase in the relative abundance of bacteria known to signal via TLR4 and Myd88 was found by Peuker *et al.* using mice as a model of genetically driven intestinal tumour formation. The microbiota and its Myd88-dependent recognition are sufficient for activation of calcineurin in CRC cells *in vitro* and are required for calcineurin-dependent tumor development *in vivo* (5). Alterations in

the tumour-associated microbiota were observed regardless of the IEC-specific deletion of calcineurin suggesting that defects in microbial stratification, as well as specific alterations in the composition of the commensal microbiota, contribute to the activation of oncogenic epithelial calcineurin. An epithelial cell-intrinsic pathway integrating signals derived from the commensal microbiota to promote intestinal tumour development was highlighted by these findings. The results support a role for microbial elements in the regulation of CRC and provide novel insight into the molecular pathways linking tumour-associated changes in the microbiota to oncogenic epithelial signaling. Their findings demonstrate that epithelial calcineurin does not regulate intestinal tumour development through effects on the composition of the commensal microbiota but rather through control of the epithelial response to changes in microbial composition and stratification along the adenoma-carcinoma sequence. Presently, only ten of the billions of human-associated microorganisms are recognized as carcinogenic by the International Agency for Cancer Research (IACR). These carcinogenic microbes include *Helicobacter pylori*, hepatitis B and C viruses, and human papillomaviruses (HPV), and are responsible for 20% of all cancers (11). Commensal bacteria of the intestinal mucosa, maintain levels of T-regulatory cells that suppress inflammation through IL-10 production (10). Immune system perturbations induced by microbiota in tissue mucosa, like that are involved in the pathology of colorectal cancer, also influence the dynamics of the resident microbial population, reducing the ability of commensal microbes to repair tissue damage and reverse inflammatory processes (12,13).

Conclusions

Peuker *et al.* (2016), concluded from the conducted elegant experiments that their studies describe a novel epithelial pathway that integrates signals derived from the commensal microbiota to promote intestinal tumor development and that may be responsive to therapeutic targeting (5). The gut microbiome is now recognized as a separate organ with distinct metabolic capacities (14,15). In the form of fecal transplants for *Clostridium difficile* infections, transplantation of the gut microbiome, has become an accepted medical practice (16). Intestinal inflammatory diseases that could lead to colorectal cancer are effectively treated with fecal transplants, and could serve as a chemo-preventative treatment (17). Just like organ transplants for various pathological conditions microbial transplantation shows promise for treating various cancers. To advance newer therapies such as synthetic designer

probiotics and microbial transplants and open novel microbiota-targeted chemotherapeutic avenues, future research will reveal specific organisms and mechanisms of cancer progression (18,19).

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Footnote

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References

- Shacter E, Weitzman SA. Chronic inflammation and cancer. *Oncology (Williston Park)* 2002;16:217-26, 229; discussion 230-2.
- Lawrence T. The nuclear factor NF-kappaB pathway in inflammation. *Cold Spring Harb Perspect Biol* 2009;1:a001651.
- Yu H, Pardoll D, Jove R. STATs in cancer inflammation and immunity: a leading role for STAT3. *Nat Rev Cancer* 2009;9:798-809.
- Ferrarelli LK. Homegrown factors in colon cancer. *Sci Signal* 2016;9:ec114.
- Peuker K, Muff S, Wang J, et al. Epithelial calcineurin controls microbiota-dependent intestinal tumor development. *Nat Med* 2016;22:506-15.
- Lee SH, Hu LL, Gonzalez-Navajas J, et al. ERK activation drives intestinal tumorigenesis in Apc(min/+) mice. *Nat Med* 2010;16:665-70.
- Rakoff-Nahoum S, Medzhitov R. Regulation of spontaneous intestinal tumorigenesis through the adaptor protein MyD88. *Science* 2007;317:124-7.
- Ryeom S, Baek KH, Rioth MJ, et al. Targeted deletion of the calcineurin inhibitor DSCR1 suppresses tumor growth. *Cancer Cell* 2008;13:420-31.
- Dotto GP. Calcineurin signaling as a negative determinant of keratinocyte cancer stem cell potential and carcinogenesis. *Cancer Res* 2011;71:2029-33.
- Liu Y, Zhang Y, Min J, et al. Calcineurin promotes proliferation, migration, and invasion of small cell lung cancer. *Tumour Biol* 2010;31:199-207.
- de Martel C, Ferlay J, Franceschi S, et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. *Lancet Oncol* 2012;13:607-15.
- Kelly D, Mulder IE. Microbiome and immunological interactions. *Nutr Rev* 2012;70 Suppl 1:S18-30.
- Hu BY, Weick JP, Yu J, et al. Neural differentiation of human induced pluripotent stem cells follows developmental principles but with variable potency. *Proc Natl Acad Sci U S A* 2010;107:4335-40.
- Zackular JP, Baxter NT, Iverson KD, et al. The gut microbiome modulates colon tumorigenesis. *MBio* 2013;4:e00692-13.
- Possemiers S, Bolca S, Verstraete W, et al. The intestinal microbiome: a separate organ inside the body with the metabolic potential to influence the bioactivity of botanicals. *Fitoterapia* 2011;82:53-66.
- Baquero F, Nombela C. The microbiome as a human organ. *Clin Microbiol Infect* 2012;18 Suppl 4:2-4.
- Khoruts A, Sadowsky MJ, Hamilton MJ. Development of fecal microbiota transplantation suitable for mainstream medicine. *Clin Gastroenterol Hepatol* 2015;13:246-50.
- Smits LP, Bouter KE, de Vos WM, et al. Therapeutic potential of fecal microbiota transplantation. *Gastroenterology* 2013;145:946-53.
- Hamm AK, Weir TL. Editorial on "Cancer and the microbiota" published in *Science*. *Ann Transl Med* 2015;3:175.

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