could also speculate that the activation of vFLIP (with or without other latent viral transcripts) at a more mature stage of B cell differentiation, such as in post-GC B cells, will permit completion of the GC reaction and better recapitulate KSHV-lymphoproliferation development. These three studies are opening up new avenues to explore the immunobiology of KSHV as it relates to its principal reservoir, B lymphocytes.

Acknowledgments

Chris Boshoff is supported by Cancer Research UK, the Medical Research Council, and the UCL/University College London Hospital Comprehensive Biomedical Research Centre.

Address correspondence to: Chris Boshoff, UCL Cancer Institute, University College London, London, United Kingdom, WC1E 6BT. Phone: 44.20.7679.6850; Fax: 44.20.7679.6817; E-mail: c.boshoff@ucl.ac.uk.

1. Alfieri C, Birkenbach M, Kieff E. Early events in Epstein-Barr virus infection of human B lymphocytes. *Virology*. 1991;181(2):595–608.
2. Myoung J, Ganem D. Active lytic infection of human primary tonsillar B cells by KSHV and its noncytolytic control by activated CD4+ T cells. *J Clin Invest*. 2011;121(3):1130–1140.
3. Hassman LM, Ellison TJ, Kedes DH. KSHV infects a subset of human tonsillar B cells, driving proliferation and plasmablast differentiation. *J Clin Invest*. 2011;121(2):752–768.
4. Ballon G, Chen K, Perez R, Tam W, Cesarman E. Kaposi sarcoma herpesvirus (KSHV) vFLIP oncoprotein induces B cell transdifferentiation and tumorigenesis in mice. *J Clin Invest*. 2011; 121(3):1141–1153.
5. Pauk J, et al. Mucosal shedding of human herpesvirus 8 in men. *N Engl J Med*. 2000;343(19):1369–1377.
6. Ambroziak JA, et al. Herpes-like sequences in HIV-infected and uninfected Kaposi's sarcoma patients. *Science*. 1995;268(5210):582–583.
7. Rappocciolo G, et al. Human herpesvirus 8 infects and replicates in primary cultures of activated B lymphocytes through DC-SIGN. *J Virol*. 2008; 82(10):4793–4806.
8. Birkmann A, et al. Cell surface heparan sulfate is a receptor for human herpesvirus 8 and interacts with envelope glycoprotein K8.1. *J Virol*. 2001; 75(23):11583–11593.
9. Chandran B. Early events in Kaposi's sarcoma-associated herpesvirus infection of target cells. *J Virol*. 2010;84(5):2188–2199.
10. Hislop AD, Taylor GS, Sauce D, Rickinson AB. Cellular responses to viral infection in humans: lessons from Epstein-Barr virus. *Annu Rev Immunol*. 2007;25:587–617.
11. Cesarman E, Chang Y, Moore PS, Said JW, Knowles DM. Kaposi's sarcoma-associated herpesvirus-like DNA sequences in AIDS-related body-cavity-based lymphomas. *N Engl J Med*. 1995;332(18):1186–1191.
12. Soulier J, et al. Kaposi's sarcoma-associated herpesvirus-like DNA sequences in multicentric Castleman's disease. *Blood*. 1995;86(4):1276–1280.
13. Dupin N, et al. Distribution of human herpesvirus-8 latently infected cells in Kaposi's sarcoma, multicentric Castleman's disease, and primary effusion lymphoma. *Proc Natl Acad Sci U S A*. 1999; 96(8):4546–4551.
14. Dupin N, et al. HHV-8 is associated with a plasmablastic variant of Castleman disease that is linked to HHV-8-positive plasmablastic lymphoma. *Blood*. 2000;95(4):1406–1412.
15. Du MQ, et al. Kaposi sarcoma-associated herpesvirus infects monotypic (IgM lambda) but polyclonal naive B cells in Castleman disease and associated lymphoproliferative disorders. *Blood*. 2001;97(7):2130–2136.
16. Kurosaki T, Aiba Y, Kometani K, Moriyama S, Takahashi Y. Unique properties of memory B cells of different isotypes. *Immunol Rev*. 2010;237(1):104–116.
17. Liu L, Eby MT, Rathore N, Sinha SK, Kumar A, Chaudhary PM. The human herpes virus 8-encoded viral FLICE inhibitory protein physically associates with and persistently activates the Ikappa B kinase complex. *J Biol Chem*. 2002;277(16):13745–13751.
18. Field N, et al. KSHV vFLIP binds to IKK-gamma to activate IKK. *J Cell Sci*. 2003;116(pt 18):3721–3728.
19. Laherty CD, Hu HM, Opipari AW, Wang F, Dixit VM. The Epstein-Barr virus LMP1 gene product induces A20 zinc finger protein expression by activating nuclear factor kappa B. *J Biol Chem*. 1992;267(34):24157–24160.
20. Suzuki T, Hirai H, Fujisawa J, Fujita T, Yoshida M. A trans-activator Tax of human T-cell leukemia virus type 1 binds to NF-kappa B p50 and serum response factor (SRF) and associates with enhancer DNAs of the NF-kappa B site and CArG box. *Oncogene*. 1993;8(9):2391–2397.
21. Derudder E, et al. Development of immunoglobulin lambda-chain-positive B cells, but not editing of immunoglobulin kappa-chain, depends on NF-kappaB signals. *Nat Immunol*. 2009;10(6):647–654.
22. Feldman AL, et al. Clonally related follicular lymphomas and histiocytic/dendritic cell sarcomas: evidence for transdifferentiation of the follicular lymphoma clone. *Blood*. 2008;111(12):5433–5439.
23. Ma SD, et al. A new model of Epstein-Barr virus infection reveals an important role for early lytic viral protein expression in the development of lymphomas. *J Virol*. 2011;85(1):165–177.

Adherent-invasive *E. coli* in Crohn disease: bacterial "agent provocateur"

Warren Strober

Mucosal Immunity Section, Laboratory of Host Defenses, National Institute of Allergy and Infectious Diseases (NIAID), NIH, Bethesda, Maryland, USA.

The role of adherent-invasive *E. coli* (AIEC) in Crohn disease (CD) has been in debate for decades. AIEC bacteria are found in the small intestine of patients with chronic CD, but it has remained unclear whether this infection is causal or secondary to underlying immune deficiencies in CD patients. In this issue of the *JCI*, Chassaing and colleagues demonstrate that AIEC bacteria express an adherence factor called long polar fimbriae (LPF) that aids in the binding of these bacteria to M cells overlying Peyer's patches and subsequent entry into lymphoid tissue. These findings provide a mechanism of AIEC penetration but do not prove that AIEC is causing a primary infection in the Peyer's patches that is necessary for the initiation or persistence of CD inflammation.

Conflict of interest: The author has declared that no conflict of interest exists.

Citation for this article: *J Clin Invest.* doi:10.1172/JCI46333.

Invasive *E. coli* as a cause of Crohn disease: a trail of research

The concept that Crohn disease (CD) is due to an infectious organism has been under investigation since this inflammation was first distinguished from mycobacterial infection some 80 years ago. While in recent decades enthusiasm for this concept has waned in the face of evidence that the disease is due to a dysregulated (and excessive) immune response against one or more commensal organisms in the intestinal microflora, creditable research is still being conducted to establish its validity. By far the most impressive example of this work is that of Darfeuille-Michaud and colleagues, who have accumulated a large body of data showing that an *E. coli* organism may be involved in CD pathogenesis. The basic findings of these investigators are as fol-

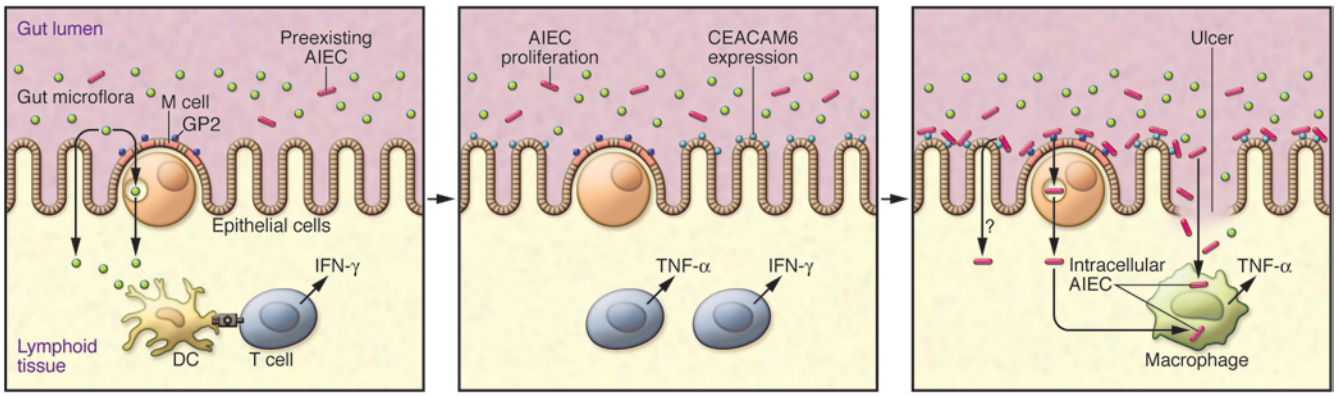

Figure 1
Proposed role of AIEC in the pathogenesis of CD. Left: CD is initiated by a genetically determined (AIEC-independent) mucosal immune response to components of the resident gut microflora; this includes the production of proinflammatory cytokines such as IL-12p70 and IFN-γ. Middle: The inflammatory response leads to increased expression of an epithelial binding site, CEACAM6, on polarized epithelial cells and thus sets the stage for the selective proliferation of preexistent *E. coli* with an AIEC phenotype. Right: AIEC bacteria enter the Peyer's patches via binding of LPF to GP2 on the surface of M cells overlying the patches; within the patches, they can exacerbate inflammation by inducing innate immune responses of patch macrophages; AIEC can also enter the lamina propria, probably via ulcerations resulting from the inflammation, and exacerbate inflammation at this site as well.

lows: (a) an adherent and invasive strain of *E. coli* (AIEC) is present in the inflamed ileum of about 22% of chronic CD patients and 36% of the newly formed terminal ilea of postsurgical patients, but only 6% of ilea in control patients; however, it is found in only a small percentage of affected colons of patients and in about 22% of the ilea of patients without ileal disease (1). (b) AIEC bacteria have type 1 pili and flagella that facilitate binding to and invasion of the epithelial cell; such binding depends on epithelial cell expression of CEACAM6, a carcinoembryonic antigen upregulated by inflammatory cytokines and possibly by the organism itself; thus, transgenic mice overexpressing CEACAM6 in epithelial cells are extensively colonized by the invasive *E. coli* and manifest colonic inflammation marked by massive neutrophil infiltration and ulceration (2–4). (c) AIEC bacteria are found in the lamina propria of patients, although this might be secondary to inflammation-induced ulcerations rather than to an independent capacity of the organisms to breach the epithelial barrier; in the lamina propria, AIEC bacteria taken up by macrophages can survive and even proliferate within macrophage vacuoles, which indicates they are not readily cleared from this site; in addition, they can induce macrophage TNF-α production and thus initiate/sustain inflammation (5, 6). (d) Genomic analysis of a representative AIEC colony (LF82) revealed that the circular genome of this *E. coli* is similar to that of several extra-intestinal pathogenic *E. coli* (ExPEC) strains, but contains genes derived from *Salmonella* and *Yersinia* organisms as well; however, while it contains several pathogenicity islands encoding a variety of virulence factors, it lacks most of the virulence genes found in ExPEC strains and thus stops short of being a virulent, acute disease–inducing agent (7).

In the current issue of the *JCI*, Chassaing et al. (the Darfeuille-Marchaud group) shed new light on the nature of AIEC (8). Previous studies by Hase et al. had shown that pathologic organisms express an operon encoding long polar fimbriae (LPF) that facilitates binding of the organism to a glycoprotein (GP2) on the surface of M cells (specialized epithelial cells on the surface of Peyer's patches through which organisms and molecules gain entry into the underlying lymphoid tissue); in addition, they showed that such binding allows entry of the bacteria into the Peyer's patches, followed by initiation of immune responses at this lymphoid site (9). In these new studies, Chassaing et al. show that AIEC bacteria express LPF and that LPF$^+$ AIEC bacteria bind to M cells and gain entry into the Peyer's patches, whereas mutant LPF$^-$ AIEC bacteria (which still have type 1 pili) do not bind to M cells or gain entry. In contrast, LPF expression is not necessary for AIEC binding to polarized enterocytes (which depends solely on CEACAM6). Turning to studies of CD patients, the authors showed that 47% of 55 CD patients harbored *E. coli* expressing an LPF with either a *Shigella* or *E. coli* (LF82) sequence, compared with 17.2% of 29 control patients. Finally, these authors showed that mice deficient for NOD2 (an intracellular sensor of a bacterial wall peptide encoded by a gene associated with increased risk for CD) express increased amounts of GP2 on M cells and thus had increased numbers of LPF$^+$ AIEC bacteria. Nevertheless, this was not associated with induction of colitis.

While previous studies had shown that one can find AIEC bacteria in the lamina propria, it was not clear that such entry was a primary event occurring before an inflammatory process had caused ulceration of the mucosa (10). The significance of these new findings is that they provide a mechanism of AIEC penetration, albeit into the Peyer's patches rather than into the lamina propria. However, this does not prove that AIEC is causing a primary infection in the Peyer's patches that is necessary for the initiation or persistence of CD inflammation. If this were the case, it would be hard to explain disease in the large intestine in all cases or in the small intestine in most cases despite the absence of AIEC. A more conservative interpretation of the findings is that the inflammatory conditions in the small intestine during the initiation of CD favors the selection and expansion of AIEC bacteria, which may then intensify the preexisting inflammation. The fact that inflammatory cytokines can induce the expression of CEACAM6 (3) supports

this view, since provision of an epithelial binding site to an organism is likely to lead to selective proliferation of small numbers of preexisting organisms with an AIEC phenotype. Similarly, loss of the antibacterial function of Paneth cells in the terminal small intestine, a known consequence of CD, could also be contributing to the emergence of AIEC (11). Finally, the view that AIEC bacteria appear in the terminal ileum as an effect rather than as a cause of the inflammation is also supported by a recently described murine model of experimental colitis occurring in T-bet/RAG2–deficient mice (so-called TRUC mice), which exhibit excessive TNF-α production and develop a "colitogenic" intestinal microflora that can transmit colitis to co-housed or cross-fostered normal mice (12). Analysis of the intestinal microflora of these TRUC mice revealed that increased colonization by *Klebsiella pneumoniae* and *Proteus mirabilis* correlated with the presence of colitis, and while these organisms by themselves did not cause colitis in germfree mice, they did cause colitis in mice with a specific pathogen–free flora (13). More to the present point, treatment of the colitis by administration of anti–TNF-α or suppressor T cells (which were absent in the RAG-deficient hosts) led to amelioration of colitis associated with either a decrease in the levels of the two implicated bacteria (anti–TNF-α treatment) or no change in these levels (suppressor cell treatment), suggesting that the inflammatory environment was causing either quantitative or qualitative alterations in the behavior of these and perhaps other organisms (13). In either case, it was apparent that the maintenance of a colitogenic microflora required the presence of an underlying (and preexisting) mucosal immune abnormality. In light of these studies, it would be interesting to determine whether AIEC persisted in the small intestine of patients successfully treated with anti–TNF-α despite amelioration of disease.

Host factors that might license AIEC pathogenesis

Since AIEC infection occurs in a substantial number of normal individuals without disease, the need for an underlying immune abnormality for the development of AIEC infection (as indicated above) may be accompanied by a similar need to license AIEC to exert pathogenic effects. One possibility here is that CD patients harbor a genetically determined immunodeficiency that renders them unable to clear organisms gaining entry to the lamina propria (such as AIEC), and the latter thus persist at this site and evoke chronic inflammation. This seems doubtful, however, given the fact that this same immunodeficiency (if it exists) doesn't cause an increased incidence of infection with true gastrointestinal pathogens such as *Shigella*, an organism that also expresses LPF that would enable it to enter the Peyer's patch; and, in fact, there is no evidence that such pathogens cause CD. Another piece of evidence against this possibility is that while NOD2-deficient mice exhibit increased entry of AIEC into Peyer's patches owing to higher numbers of GP2-expressing M cells and, in general, manifest decreased epithelial barrier function, these mice do not develop colitis upon challenge with AIEC (14). This finding relates to the possibility that an underlying immunodeficiency enables AIEC-induced inflammation, because NOD2 deficiency has been associated with decreased capacity to kill intracellular organisms due to defective autophagy and that AIEC bacteria manifest enhanced proliferation in cells with a defect in autophagy due to ATG16L1 deficiency (15, 16). Thus, the failure of AIEC to cause colitis in NOD2-deficient mice suggests that subtle immunodeficiency such as that possibly caused by NOD2 dysfunction does not predispose to an AIEC-mediated colitis.

A consensus model of CD

Another underlying genetically determined abnormality (or class of abnormalities) that could increase the potential of AIEC to induce inflammation relates to the now dominant hypothesis of CD pathogenesis, alluded to above, that holds that the disease is due to a genetically determined hyperreactivity to normal commensal microflora in the gastrointestinal tract. The very powerful evidence in favor of this concept includes the fact that colitis can be induced in mice with a specific pathogen–free microflora and not in the absence of a microflora (17). In addition, the best-characterized genetically determined risk factors now identified through genome-wide searches, the aforementioned NOD2 polymorphism, is thought to act by inactivation of a normal brake on innate (TLR-induced) enhancement of mucosal immune responses (18, 19). Finally, and perhaps most importantly, extensive studies of the colonic bacterial flora in CD have not revealed the presence of potentially pathogenic organisms; on the contrary, they have revealed deletions of certain bacterial groups that could result in loss of organisms that ordinarily induce suppressor or inhibitory responses so that, again, the microfloral changes encourage immunologic hyperresponsiveness (20, 21). In conclusion, therefore, the most likely scenario for AIEC activity is that CD is initiated by a dysregulated response to normal intestinal organisms and this creates an inflammatory milieu that favors expansion and invasion of AIEC in some patients; the latter then contribute to the inflammation by serving as an organism that has a prominent role in feeding the underlying immune hyperresponsiveness (Figure 1).

Address correspondence to: Warren Strober, NIH Campus, Clinical Research Center, 9000 Rockville Pike, 5 West, Rm 3940, Bethesda, Maryland 20892, USA. Phone: 301.496.6810; Fax: 301.402.2240; E-mail: Wstrober@niaid.nih.gov.

1. Darfeuille-Michaud A, et al. High prevalence of adherent-invasive *Escherichia coli* associated with ileal mucosa in Crohn's disease. *Gastroenterology*. 2004;127(2):412–421.
2. Barnich N, Boudeau J, Claret L, Darfeuille-Michaud A. Regulatory and functional co-operation of flagella and type 1 pili in adhesive and invasive abilities of AIEC strain LF82 isolated from a patient with Crohn's disease. *Mol Microbiol*. 2003;48(3):781–794.
3. Barnich N, et al. CEACAM6 acts as a receptor for adherent-invasive *E. coli*, supporting ileal mucosa colonization in Crohn disease. *J Clin Invest*. 2007;117(6):1566–1574.
4. Carvalho FA, et al. Crohn's disease adherent-invasive *Escherichia coli* colonize and induce strong gut inflammation in transgenic mice expressing human CEACAM. *J Exp Med*. 2009;206(10):2179–2189.
5. Kleessen B, Kroesen J, Buhr HJ, Blaut M. Mucosal and invading bacteria in patients with inflammatory bowel disease compared with controls. *Scand J Gastroenterol*. 2002;37(9):1034–1041.
6. Glasser AL, Boudeau J, Barnich N, Perruchot MH, Columbel JF, Darfeuille-Michaud A. Adherent invasive *Escherichia coli* strains from patients with Crohn's disease survive and replicate within macrophages without inducing host cell death. *Infect Immun*. 2001;69(9):5529–5537.
7. Miquel S, et al. Complete genome sequence of Crohn's disease-associated adherent-invasive *E. coli* strain LF82. *PLoS One*. 2010;5(9):e12714.
8. Chassaing B, et al. Crohn disease–associated adherent-invasive *E. coli* bacteria target mouse and human Peyer's patches via long polar fimbriae. *J Clin Invest*. 2011;121(3):966–975.
9. Hase K, et al. Uptake through glycoprotein 2 of FimH(+) bacteria by M cells initiates mucosal immune response. *Nature*. 2009;462(7270):226–230.
10. Kleessen B, Kroesen AJ, Buhr HJ, Blaut M. Mucosal and invading bacteria in patients with inflammatory bowel disease compared with controls. *Scand J Gastroenterol*. 2002;37(9):1034–1041.
11. Simms LA, Doecke JD, Walsh MD, Huang N, Fowler EV, Radford-Smith GL. Reduced α-defensin expression is associated with inflammation and not NOD2 mutation status in ileal Crohn's disease. *Gut*. 2008;57(7):903–910.

12. Garrett W, et al. Communicable ulcerative colitis induced by T-bet deficiency in the innate immune system. *Cell*. 2007;131(1):33–45.
13. Garrett WS, et al. Enterobacteriaceae act in concert with the gut microbiota to induce spontaneous and maternally transmitted colitis. *Cell Host Microbe*. 2010;8(3):292–300.
14. Barreau F, et al. Nod2 regulates the host response towards microflora by modulating T cell function and epithelia permeability in mouse Peyer's patches. *Gut*. 2009;59(2):207–217.
15. Lapaquette P, Glasser A-L, Huett A, Xavier RJ, Darfeuille-Michaud A. Crohn's disease-associated adherent-invasive *E. coli* are selectively favoured by impaired autophagy to replicate intracellularly. *Cell Microbiol*. 2010;12(1):99–113.
16. Cooney R, et al. NOD2 stimulation induces autophagy in dendritic cells influencing bacterial handling and antigen presentation. *Nat Med*. 2010; 16(1):90–97.
17. Strober W, Fuss IJ, Blumberg RS. The immunology of mucosal models of inflammation. *Annu Rev Immunol*. 2002;20:495–549.
18. Watanabe T, et al. Muramyl dipeptide activation of nucleotide-binding oligomerization domain 2 protects mice from experimental colitis. *J Clin Invest*. 2008;118(2):545–559.
19. Strober W, Fuss IJ, Mannon P. The fundamental basis of inflammatory bowel disease. *J Clin Invest*. 2007;117(3):514–521.
20. Frank D, St. Amand AL, Feldman RA, Boedeker EC, Harpaz N, Pace NR. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. *Proc Natl Acad Sci U S A*. 2007;104(34):13780–13785.
21. Takaishi H, et al. Imbalance in intestinal microflora constitution could be involved in the pathogenesis of inflammatory bowel disease. *Int J Med Microbiol*. 2008;298(5–6):463–472.

RAS signaling pathway mutations and hypertrophic cardiomyopathy: getting into and out of the thick of it

Bruce D. Gelb[1] and Marco Tartaglia[2]

[1]Child Health and Development Institute, Mount Sinai School of Medicine, New York, New York, USA. [2]Dipartimento di Ematologia, Oncologia e Medicina Molecolare, Istituto Superiore di Sanità, Rome, Italy.

In this issue of the *JCI*, Wu et al. and Marin et al. describe two new mouse models of inherited disorders of the RAS/MAPK signal transduction pathway that display hypertrophic cardiomyopathy (HCM); the model from the former paper was from a gain-of-function *Raf1* mutation, and the model from the latter paper was from a protein tyrosine phosphatase, non-receptor type 11 (*Ptpn11*) mutated allele encoding Shp2 with impaired catalytic function. The two groups show that HCM arises from increased signaling through Erk1/2 and the mTor complex 1, respectively, and that those cardiac issues can be prevented or reversed with small-molecule therapies inhibiting the appropriate pathway. Aside from being the first studies of treatment for Noonan syndrome and related disorders in a mammalian system, these papers provide important insights into the role of RAS signaling in cardiac hypertrophy and suggest the complexity in developing meaningful therapy for individuals with these RASopathies.

Signaling initiated by extracellular ligands, such as growth factors and cytokines, that is transduced through RAS proteins to multiple effectors, including the MAPKs, is central to cell proliferation, survival, differentiation, metabolism, and migration. The paradigmatic RAS/MAPK pathway (Figure 1) involves RAF proteins, particularly RAF1 and BRAF, which are MAPK kinase kinases that are activated after binding to RAS-GTP and then activate MAPK kinases, MEK1 and MEK2, which, in turn, activate the MAPKs, ERK1 and ERK2. Since its discovery nearly 30 years ago (1), the enormous role of perturbed RAS/MAPK signaling in cancer biology has become evident. Specifically, more than 30% of human cancers include mutations in genes encoding proteins in this pathway, particularly RAS proteins and BRAF. The vast majority of these genetic defects are acquired and result in increased activation of ERK1/2, often through gain-of-function alterations of the mutant proteins.

The importance of increased RAS/MAPK signaling in cancer spurred efforts to develop novel therapies that can reduce it (2). One strategy is to inhibit the mutant protein specifically. The best example of that approach is the ongoing work with PLX4032 (also known as RO5185426), which targets the $BRAF^{V600E}$, the most common oncoprotein implicated in melanoma (3). Successful phase I and II clinical trials with malignant melanoma have been completed, and a phase III trial is ongoing (4). However, the more common approach has been to develop small molecules that inhibit RAS/MAPK signaling broadly. Products of this track have included the farnesyl transferase inhibitors, which are intended to reduce RAS translocation to the cell membrane, a necessary step for signaling, and inhibitors of RAF and MEK activities. To date, these efforts have been less successful (5). Since RAS/MAPK signaling is present in a wide array of normal cells and RAS proteins control multiple cellular processes and have several downstream effectors, titrating the right level of inhibition to provide therapeutic efficacy without incurring intolerable side effects is challenging. Indeed, clinical trials with PD325901, which is a highly specific MEK inhibitor, were terminated early due to ophthalmologic and neurologic toxicity, despite the fact that MEK1/2 are downstream in the RAS pathway and are only known to activate ERK1/2 (6).

After the discovery of the RAS/MAPK pathway, studies with model organisms like *Drosophila melanogaster* and *Caenorhabditis elegans* elaborated its central role in organismal development (7, 8). Subsequent experiments with loss-of-function alleles and cancer-related gain-of-function mutations, particularly in mouse models, generally produced one of two outcomes. For some genes

Conflict of interest: Bruce D. Gelb and Marco Tartaglia receive royalties from several commercial laboratories for *PTPN11* and *RAF1* mutation testing for Noonan syndrome.

Citation for this article: *J Clin Invest.* doi:10.1172/JCI46399.