Published in final edited form as:

Nature. 2016 November 10; 539(7628): 173–175. doi:10.1038/nature19479.

Blood Cancer: Bad Neighbours Cause Bad Blood

Gordon Chan and

Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario M5S 3M2, Canada

Benjamin G. Neel

Laura and Isaac Perlmutter Cancer Center, New York University Langone Medical Center, New York, New York 10016, USA

Abstract

Expression of a blood-cancer-associated genetic mutation only in the non-blood cells of the bone marrow is sufficient to cause blood cancer in mice. This finding might point to new approaches to treating an often-fatal disease. See Letter p.XXX

Mutations in blood stem cells can result in excessive production of one or more types of mature blood cell and a type of cancer called myeloproliferative neoplasm (MPN). One such disorder is juvenile myelomonocytic leukemia (JMML), a rare paediatric MPN characterized by expansion of the white blood cell compartment¹. Currently, JMML can be remedied only by stem-cell transplantation, but about 50% of patients relapse following this treatment. A more detailed understanding of the disease could lead to new therapies and improved outcomes. In a paper online in *Nature*, Dong *et al.*² report that mutation of the gene *Ptpn11* in the non-blood cells that surround blood stem cells causes a JMML-like myeloproliferative neoplasm (a type of white blood cell cancer) in mice, owing to altered interactions between these two cell types.

Mutations in genes that encode proteins of the RAS–ERK signalling pathway are found in the blood cells (but no other cells) of about 90% of patients with sporadic JMML^{1,3}. The most frequent of these occur in the gene *PTPN11*. Such mutations activate the enzyme encoded by *PTPN11*, SHP2, increasing RAS–ERK signalling. Certain *PTPN11* mutations can be inherited, and so present in all cells of the body, giving rise to the developmental disorder Noonan Syndrome⁴. Noonan syndrome is characterized by cardiac, facial, cognitive and growth abnormalities, but about 20% of affected children have abnormal white blood cell counts, and a few develop a congenital form of JMML.

Previous studies of JMML have focused on the effects of disease-associated *PTPN11* in blood cells, and have established that expression of the mutant gene in these cells alone can promote development of a JMML-like MPN in mice^{5,6}. Dong *et al.* confirmed that blood cell-restricted expression of mutant *Ptpn11* causes MPN (Fig. 1a). They next studied mice that harbour *Ptpn11* mutations only in stromal (i.e., non-blood) cell types of the bone marrow, which surround the developing blood cells—surprisingly, these mice, which have *genetically normal* blood cells, develop a disease similar to congenital JMML, in which the mutant gene is present in all tissues.

The authors find that mutant *Ptpn11* can only give rise to MPN when expressed in certain types of stromal cells of the bone marrow (mesenchymal stem cells and the bone progenitors that they give rise to) but not in others (mature bone or blood-vessel cells). Furthermore, if genetically normal blood stem cells reside long enough in this noxious microenvironment, they become fully cancerous and can give rise to MPN when transplanted into healthy mice. Presumably, the abnormal microenvironment induces mutations (genetic alterations) or epigenetic changes (which affect gene expression without changing DNA sequence) in normal blood stem cells that result in this transformation.

What these changes in normal blood cells are — and whether they affect RAS–ERK pathway genes — is an interesting question that is left unresolved. Perhaps clarifying this issue would shed light on the causes of the approximately 5 to 10% of JMML cases for which a genetic basis remains undefined¹. For example, might these cancers be caused by mutations in mesenchymal stem cells, rather than blood stem cells?

The finding that an abnormal bone-marrow microenvironment can promote blood disease is not unprecedented: a variety of genetic alterations can evoke MPN or acute leukemia when engineered into the bone marrow stromal cells of mice⁷. But Dong and colleagues model an actual human disease (JMML associated with Noonan syndrome) in which an aberrant bone marrow microenvironment is present from birth. Their results therefore suggest that an abnormal bone-marrow microenvironment might provide the initial, and potentially the more potent, MPN-promoting stimulus in congenital JMML.

The levels of SHP2 activation caused by *PTPN11* mutation in patients can vary^{1,3}. In people with Noonan syndrome, only the most activating mutations cause JMML. Perhaps under such circumstances, JMML can only develop when blood cells and the stromal microenvironment both bear the mutant gene. A similar requirement has been reported for another mouse model of MPN caused by a distinct type of genetic defect⁸.

Dong *et al.* find that several pro-inflammatory factors produced by mutant stromal cells, including the protein CCL3, are present in blood serum from their mice and from patients with Noonan syndrome. These findings suggest that such factors could serve as biomarkers to identify children at increased risk of JMML. Furthermore, the authors find that drugs that block CCL3 action decrease MPN development in mice (Fig. 1b). Administering such drugs to such high-risk patients might spare them from transplantation.

The current study also has potential implications for sporadic JMML. Previous studies showed that aberrant blood cells can send signals to stromal cells that alter the bone-marrow microenvironment to favour their own expansion or to impede the survival, proliferation and function of normal blood stem cells⁷. Dong *et al.* find that *Ptpn11* mutant blood cells also produce pro-inflammatory factors, suggesting a vicious cycle in which mutant blood cells perturb the microenvironment, which, in turn, augments expansion of the cancerous blood-cell population. If bone-marrow stromal cells have been rendered abnormal by cancerous blood cells in sporadic JMML, persistence of this abnormal microenvironment might contribute to disease recurrence after stem-cell transplant.

Consequently, perhaps the most immediate intervention suggested by Dong and colleagues' work is to investigate the effects of CCL3 blockers in transplant regimens for JMML patients. One such drug, Maraviroc, is used to treat HIV infection, and also blocks graft versus host disease (a complication of bone marrow transplantation)⁹. The authors find that such agents are more effective at preventing MPN post-transplant than in combatting established JMML in mice. Nevertheless, combining these blockers with targeted therapies aimed at reversing the effects of increased RAS–ERK activation also could represent a promising new therapeutic strategy for JMML.

Finally, the results of the current study resonate with, and inform, emerging themes in cancer biology. It is becoming clear that the interactions between cancerous cells and their microenvironment determine cancer behaviour and response to therapy. We also know that inflammation can initiate, as well as enhance, cancer. In solid tumours, one major effect of tumour-associated inflammation is to suppress the host immune system¹⁰. It will be interesting to see whether therapies directed against the JMML microenvironment evoke or augment an anti-MPN immune response.

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Figure 1. Collaboration causes blood cancer

a, Mutation in the gene *Ptpn11* in the blood cells of mice and humans cause the cancer juvenile myelomonocytic leukemia (JMML), which is one of a family of “myeloproliferative neoplasms” (MPNs). The stromal cells that surround developing blood cells do not need to be mutated for sporadic JMML development. **b**, However, Dong et al. report that expression of mutant *Ptpn11* in the stroma causes MPN in mice. These mice provide insight into a congenital form of JMML in which the mutation is present in all cells. The mutant stromal cells produce pro-inflammatory factors, including the protein CCL3, which cause cancerous transformation of normal blood cells into cells of a JMML-like MPN. Stromainduced MPN can be ameliorated (dashed lines) by drugs that block CCL3 action.