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BCR–ABL and *CDKN2A*: a dropped connection

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In their recent Review of chronic myeloid leukamia (CML) stem cell biology (Savona, M. & Talpaz, M. Getting to the stem of chronic myeloid leukemia. *Nature Rev. Cancer* **8**, 341–350)[1], Savona and Talpaz focus their attention exclusively on deregulated self-renewal mechanisms in Philadelphia chromosome (Ph)$^+$ hematopoietic stem cells (HSCs) in chronic-phase CML and on the role of β-catenin abnormalities in granulocyte–macrophage progenitors in myeloid blast crisis. However, a review of genomic abnormalities in lymphoid blast crisis provides insights into alternative mechanisms of progenitor self-renewal in BCR–ABL-driven diseases. Deletion of the *CDKN2A* locus (encoding the *INK4A* and *ARF* tumour suppressor genes) frequently occurs in the progression of CML from chronic-phase to lymphoid, but not myeloid, blast crisis[2], and a recent genome-wide analysis[3] (published concurrently with this CML review) has reinforced the conclusions of earlier studies. *INK4A* and *ARF* share common second and third exons, are translated in alternate reading frames, and exhibit no sequence similarity[4]. Whereas $p16^{INK4A}$ is a *bona fide* cyclin-dependent kinase inhibitor, $p14^{ARF}$ ($p19^{Arf}$ in mice) is not, but instead regulates p53 tumour suppressor function through its interaction with MDM2 (REF. 5). BCR–ABL induces $p19^{Arf}$ *in vivo* to oppose tumour development, but the combination of BCR–ABL expression and *Arf* inactivation is sufficient to generate leukaemia-initiating cells in a murine model of Ph$^+$ acute lymphocytic leukaemia[6]. Therefore, in BCR–ABL-driven lymphoid leukaemias — specifically, CML lymphoid blast crisis and Ph$^+$ acute lymphocytic leukaemia — deletion of *INK4A* and *ARF* in committed Ph$^+$ lymphoid blasts is expected to simultaneously disrupt both the RB and p53 tumour suppressor networks, thereby facilitating leukaemia-initiating cell self-renewal and enhancing targeted therapeutic resistance *in vivo*.

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