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Cell-cycle deregulation in progressive CML

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There are alternative splice variants for *CDKN2A* and, in their correspondence on our Review (Savona, M. & Talpaz, M. Getting to the stem of chronic myeloid leukemia. *Nature Rev. Cancer* **8**, 341–350), Williams and Sherr correctly note that one of these variants is translated through an alternate reading frame (hence, *ARF*), which acts by stabilizing p53 protein levels by inhibiting MDM2-mediated ubiquination and degradation[1,2]. We apologize for oversimplifying this molecular biology; indeed, *ARF* does not inhibit cyclin-dependent kinases (specifically, CDK4 and CDK6) as *INK4A* does, and we thank Williams and Sherr for clarifying this point. We failed to describe this important nuance in our efforts to express the known direct relationships between BCR–ABL and these tumour suppressors, their influence on G1 in the cell cycle, and their net pro-senescence effects. This was the planned design of the discussion on tumour suppressors in the latter half of our manuscript[3].

Absence of the *CDKN2A* locus is a popular theme in liquid malignancies, and has been noted as a hallmark of aggressive disease in lymphocytic leukaemias for many years.[4,5] At this point, it is still not clear whether the *CDKN2A* locus is deleted solely in lymphoid blast crisis, and not myeloid blast crisis chronic myeloid leukaemia (CML), as Williams and Sherr contend. There are early experimental data of loss of this locus also in myeloid malignancies[6–8], and recent genomic analyses do not expressively indicate that this aberrancy is germane to lymphoid blast crisis, and exclusive of myeloid blast crisis or the rare entity Philadelphia chromosome (Ph)$^+$ acute myeloid leukaemia (AML)[9,10]. That said, the authors have provided clear evidence that aberrancy of the *CDKN2A* locus is common and important in lymphoid leukaemias.

Likewise, we recognize the burgeoning data that the lack of the *CDKN2A* locus combined with BCR–ABL is sufficient to generate committed cells capable of self-renewal in a murine model of Ph$^+$ acute lymphocytic leukaemia (ALL)[9,10]. Though there is description of BCR–ABL-positivity and concomitant loss of $p16^{INK4A}$ and $p14^{ARF}$ in patients with Ph$^+$ acute leukaemias (and even some correlations with prognosis)[11], it has not yet been illustrated whether this interaction is direct, dependent and sequential *in vivo*, and not part of a cascade of progressive genetic instability. It is likely that a disruption of this and other cell cycle checkpoint kinases are part of many subsequent events that influence disease phenotype and progression. In the discussion of the carcinogenesis of CML, FIG. 3 of our paper[3] was intended to, first, illustrate one example of an established tumour suppressor pathway(s) that BCR–ABL directly influences and, second, describe a known influence of epigenetic phenomena. In this light, data supporting the direct cause-and-effect relationship between BCR–ABL and tumour suppressors from the *CDKN2A* locus as CML progresses are tenuous.

Finally, we reiterate the tenant of an anaplastic threshold (see FIG. 1 of the manuscript)[3], which embodies our theory of carcinogenesis in CML: initially in the disease, and prior to the anaplastic threshold, BCR–ABL is a dominant oncogene on which the leukaemia cell depends for survival, and elimination of BCR–ABL — through imatinib, or other tyrosine kinase inhibitors — leads to remission; next, as the genetic instability grows, the disease approaches the anaplastic threshold — a period of transition at which the intracellular chaos induced by BCR–ABL begins to allow the leukaemic phenotype to be sustained irrespective of BCR–ABL; and, finally, there is a period of disease progression clearly beyond the anaplastic threshold in which BCR–ABL is superfluous and the leukaemic genotype can self-sustain the leukaemic phenotype. This leukaemic genotype is akin to that described in the recent genetic studies of advanced CML and Ph$^+$ ALL[12,13]. The difficulty of treating advanced CML lies in the fact that, at this point, BCR–ABL is just one member of an angry mob inciting anarchy, and not just a lone suppressible agitator.

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