INNATE IMMUNE CELLS

A *Morrbid* way of stayin' alive

The lifespan of short-lived myeloid cells — that is, neutrophils, eosinophils and 'classical' monocytes — must be tightly regulated to maintain a protective immune response while minimizing host damage caused by prolonged inflammation. Several factors, including pro-survival cytokines, can influence the lifespan of these cells but the precise molecular mechanisms involved remain unknown. Reporting in *Nature*, Kotzin *et al.* describe a newly identified long non-coding RNA (lncRNA), which they termed *Morrbid* (myeloid RNA regulator of BIM-induced death), that regulates the lifespan of short-lived myeloid cells in response to extracellular pro-survival signals through the suppression of the pro-apoptotic gene *BCL2L11* (also known as BIM).

“*Morrbid* regulates *Bcl2l11* expression and thus short-lived myeloid cell survival

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Analysis of multiple RNA sequencing datasets for lncRNAs identified a previously uncharacterized lncRNA that is conserved across species and is specifically expressed by mature neutrophils, eosinophils and classical (LY6C^{hi}) monocytes in both mice and humans. To investigate the function of this lncRNA (termed *Morrbid*), the authors generated *Morrbid*-deficient mice and found that the numbers of neutrophils, eosinophils and LY6C^{hi} monocytes, but not of other immune cell populations, were greatly reduced in the blood and tissues of these mice. Furthermore, these mice were highly susceptible to *Listeria monocytogenes* infection and were protected in a model of eosinophil-mediated allergic lung inflammation. These data indicate a specific role for *Morrbid* in the homeostasis of short-lived myeloid cells.

Further analysis showed that the number of mature short-lived myeloid cells, but not their progenitors, was greatly reduced in the bone marrow of *Morrbid*-deficient mice and that they were highly prone to apoptosis in *ex vivo* culture. In addition, the authors observed a ~2-fold decrease in the half-life of remaining neutrophils in *Morrbid*-deficient mice compared with wild-type controls, indicating a role for *Morrbid* in regulating apoptosis in short-lived myeloid cells.

Many lncRNAs function by regulating neighbouring genes; *Morrbid* is located ~150 kb upstream of *Bcl2l11*, which led the authors to analyse the regulation of this pro-apoptotic gene. Protein and mRNA levels of *Bcl2l11* were greatly increased in neutrophils, eosinophils and LY6C^{hi} monocytes

from *Morrbid*-deficient mice and additional *in vitro* studies confirmed that *Morrbid* regulates *Bcl2l11* expression and thus short-lived myeloid cell survival.

Next, the authors showed that the pro-survival cytokines of the β -chain family (IL-3, IL-5 and GM-CSF) induce the expression of *Morrbid*, resulting in a corresponding repression of *Bcl2l11* in short-lived myeloid cells. Furthermore, eosinophils from patients with hypereosinophilic syndrome, which are known to have an extended lifespan, expressed significantly higher levels of *MORRBID* than cells from healthy controls and this expression correlated with plasma IL-5 levels.

An analysis of the molecular mechanisms by which *Morrbid* regulates *Bcl2l11* expression showed that the lncRNA promotes the deposition of repressive histone marks (H3K27me3) and the enrichment of polycomb repressive complex 2 (PRC2) at the *Bcl2l11* promoter. Furthermore, *Morrbid* was shown to specifically function in *cis* to repress *Bcl2l11*. Additional results suggested a model in which *Morrbid* proximity to *Bcl2l11*, mediated through DNA looping, enables *Morrbid* RNA to promote PRC2 enrichment within the *Bcl2l11* promoter through direct *Morrbid*-PRC2 interactions and possibly through other indirect mechanisms.

Together, these data indicate that the newly described lncRNA *Morrbid* functions in an allele-specific manner to suppress *Bcl2l11* expression in neutrophils, eosinophils and LY6C^{hi} monocytes, providing a mechanism that allows for the rapid control of apoptosis in response to pro-survival signals.

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