MICROENVIRONMENT

Secreted DNA damage?

> chromatin fragments from leukaemic blasts induce a DNA damage response in recipient cells

When leukaemia progresses to an acute phase, leukaemic blasts egress from the bone marrow to the peripheral blood, but how this transit through the bone marrow microenvironment occurs is unknown. Dvoráková and colleagues used a chicken model of MYB-induced acute myeloid leukaemia (AML) to investigate.

MYB$^+$ AML blasts egress rapidly from bone marrow, and this is accompanied by the destruction of growth plate structures in the bone. MYB$^+$ AML blasts caused the death of bone marrow stromal cells in co-culture through the release of soluble factors. So, the authors compared the secretome of MYB$^+$ AML blasts with controls and found that there was a substantial increase in the secretion of chromatin fragments by MYB$^+$ AML blasts. Similarly, four human AML samples from bone marrow aspirates also secreted chromatin fragments.

What happens to these secreted chromatin fragments? BrdU-labelled DNA from MYB$^+$ AML blasts was present in the nuclei of bone marrow cells and fibroblasts after co-culture. Fragments of chromatin have two DNA ends, which are substrates for DNA damage response signalling. Consistently, phosphorylated histone H2AX (known as γH2AX), an early event in DNA damage response signalling, was detected in cells that were co-cultured with MYB$^+$ AML blasts or with the secreted chromatin extracts. Furthermore, immunofluorescence analyses revealed that BrdU-labelled DNA and γH2AX colocalized, indicating that chromatin fragments from leukaemic blasts induce a DNA damage response in recipient cells.

Does secreted chromatin facilitate bone marrow egress? The authors found that the presence of secreted DNA in fibroblast nuclei correlated with activation of caspase 3 and morphological features of cell death. This was prevented when the chromatin extracts were pretreated with micrococcal nuclease to digest the DNA, indicating that the cytotoxicity directly resulted from the ingress of the DNA fragments. Interestingly, the authors also showed that DNA fragments were incorporated into genomic DNA of recipient cells that were treated with ionizing radiation (to introduce DNA double-strand breaks), indicating that secreted DNA fragments may also disrupt genetic loci.

There is increasing evidence that circulating DNA, whether in the form of chromatin or in exosomes or vesicles, has a role in promoting metastasis of solid tumours by affecting stromal cells in the bone marrow and at distant sites. However, how this is facilitated by circulating DNA remains unclear. This paper provides evidence of a possible mechanism: the uptake of DNA by recipient cells and the subsequent activation of DNA damage responses that lead to cell death.

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ORIGINAL RESEARCH PAPER Dvoráková, M. *et al.* DNA released by leukemic cells contributes to the disruption of the bone marrow microenvironment. *Oncogene* 10 Dec 2012 (doi:10.1038/onc.2012.553)