

Invited Speaker Abstract

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The bone microenvironment and myeloproliferative disease

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Myeloproliferative diseases (MPDs) are blood cell diseases that are considered to be intrinsic to haematopoietic cells. We recently demonstrated that mice null for retinoic acid receptor gamma ($RAR\gamma$) had an MPD that was not intrinsic to haematopoietic cells, but instead was induced by the $RAR\gamma$ deficient bone marrow microenvironment. The MPD phenotype continued for the lifespan of the mice and was more pronounced over time, with the severity of the disease correlating with marked loss of trabecular bone in the mice. Interestingly, we observed active haematopoiesis occurring in adipose tissue of these older mice, suggesting fat is an additional site for extramedullary haematopoiesis.

Transplant studies revealed the MPD was not intrinsic to the haematopoietic cells. In contrast, wildtype haematopoietic cells transplanted into $RAR\gamma$ null mice rapidly developed an MPD that was more profound than that observed in non-transplanted $RAR\gamma$ mutants. Secondary transplant studies from such mice revealed that an $RAR\gamma$ null microenvironment was absolutely required to sustain this MPD: the MPD phenotype reverted to normal in wildtype secondary recipients but remained severe in $RAR\gamma$ null secondary recipients.

Additional studies revealed that elevated $TNF\alpha$ contributed to the disease, but that other factors were also contributing to the microenvironment-induced MPD. We are currently further investigating the contribution of $TNF\alpha$ to both the bone and MPD phenotypes in these mice.

These data show that loss of $RAR\gamma$ results in a non-haematopoietic cell intrinsic MPD, revealing the capability of the microenvironment to induce haematopoietic disorders previously considered to be exclusively intrinsic to haematopoietic cells.