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MYELOFIBROSIS INDUCED BY THE GATA-1^{low} MUTATION: EFFECTS OF THE GENETIC BACKGROUND.

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Mice harboring the GATA-1^{low} mutation in the CD1 background develop, while aging, myelofibrosis, a syndrome similar to human idiopathic myelofibrosis. The disease manifests itself at 10 months with marrow fibrosis while a clear picture (anemia, tear drop poikilocytes and progenitor cells in blood, marrow and spleen fibrosis and extramedullary hemopoiesis in liver) is observed from 12 months onward (Vannucchi et al., Blood 100: 1123-1132, 2002). In the CD1 background, the trait is dominant and is expressed by homozygote and heterozygotes females alike with 100% penetrance. Since GATA-1 is located on the X chromosome, in heterozygote females, the stem cell clone expressing the mutant allele must have a proliferative advantage over that expressing the normal allele. In mouse, the stem cell proliferation activity is genetically controlled, with C57BL/6, CD1 and DBA2 background conferring the lowest, intermediate and highest activity, respectively. To assess the possible effect of the stem cell proliferative activity on the capacity of the GATA-1^{low} mutation to induce myelofibrosis, the GATA-1^{low} mutation was crossed in the three backgrounds and the heterozygote F1 female offspring sacrificed at 12 months of age to analyze the development of the disease. All the mice (independently from background) expressed an hematocrit of 46-48% and platelet counts of 3.4-4.1x10^5/microL. However, they differed greatly for other markers of myelofibrosis: DBA2 F1 females did not contain poikilocytes in blood and expressed limited marrow and spleen fibrosis. In contrast, C57BL/6 F1 females contained many poikilocytes in blood, expressed extensive marrow and spleen fibrosis, massive osteogenesis and extramedullary hemopoiesis in liver. The phenotype of CD1 F1 females was intermediate between these two. These results indicate that, although the myelofibrosis induced by the GATA-1^{low} allele is a dominant trait, the progression of the disease is profoundly affected by the background harboring the mutation.