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Brief communication

Polμ deficiency induces moderate shortening of P53$^{-/-}$ mouse lifespan and modifies tumor spectrum

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ABSTRACT

Non-homologous end joining (NHEJ) is the main mechanism for double strand break (DSB) DNA repair. The error-prone DNA polymerase mu (*Polμ*) is involved in immunoglobulin variable region rearrangement and in general, NHEJ in non-lymphoid cells. Deletion of NHEJ factors in *P53*$^{-/-}$ mice, which are highly prone to development of T cell lymphoma, generally increases cancer incidence and shifts the tumor spectrum towards aggressive pro-B lymphoma. In contrast, *Polμ* deletion increased sarcoma incidence, proportionally reducing pro-B lymphoma development on the *P53*-deficient background. Array comparative genomic hybridization (aCGH) analyses showed DNA copy number alterations in both *P53*$^{-/-}$ and *Polμ*$^{-/-}$*P53*$^{-/-}$ lymphomas. Our results also indicate that the increase in sarcoma incidence in *Polμ*$^{-/-}$*P53*$^{-/-}$ mice could be associated with *Cdk4* and *Kub3* amplification and overexpression. These results identify a role for *Polμ* in the prevention of sarcomagenesis on a murine *P53*-deficient background, in contrast to most other NHEJ factors.

1. Introduction

Double strand breaks (DSB) are a highly deleterious form of DNA damage linked to genomic instability, cell death, senescence and oncogenic transformation [1–3]. The two principal mechanisms for DSB repair are homologous recombination (HR) and non-homologous end joining (NHEJ) [4]. There are five 'core' NHEJ factors, *Ku*, *DNA-PKcs* and the complex *LigIV-XRCC4-XLF*. When DSB are not directly rejoinable, these core proteins are aided by 'accessory' NHEJ factors that process the break-ends before ligation, including the nuclease Artemis, and the DNA polymerases mu (*Polμ*) and lambda (*Polλ*) [5,6]. Mice lacking one of the core NHEJ factors other than *XLF* show severe immunodeficiency due to blocked B and T lymphocyte development, which renders the animals sensitive to ionizing radiation [7–14]; these mice also show premature aging phenotypes [15–17].

Polμ is an error-prone enzyme of the PolX family, which also includes *Polλ* and TdT [18]. *Polμ* and *Polλ* play key roles in classically defined NHEJ, and are broadly expressed, with highest expression in hematopoietic tissue and testis, respectively [18–20]. *Polμ* is necessary *in vivo* for correct recombination of the immunoglobulin κ light chain during B cell development [21]. Additionally, *Polμ*-deficient mice are hypersensitive to ionizing radiation and show altered steady-state hematopoiesis [22,23]. We also identified a positive role for *Polμ* deficiency in the functional maintenance of brain [24] and liver [25].

The *P53*$^{-/-}$ mouse is the most widely used transgenic model for cancer study. These mice are highly cancer-prone; most succumb to aggressive thymic lymphomas (~70%) and to a markedly lesser extent (~25%), also develop sarcomas [26]. Instead of characteristic T lymphoma, most NHEJ$^{-/-}$*P53*$^{-/-}$ strains develop pro-B lymphoma, usually associated with a specific translocation between the *IgH* enhancer locus and *c-Myc* [8,27–29]. Only *XLF*$^{-/-}$*P53*$^{-/-}$ mice are not markedly prone to pro-B lymphoma development, but to medulloblastomas [10]. To further study *Polμ* function in *in vivo* tumor development, we generated *Polμ*$^{-/-}$*P53*$^{-/-}$ mice, which had a moderate shorter lifespan than *P53*$^{-/-}$ mice, associated with higher sarcoma incidence. Sarcomas from these mice showed a characteristic genome amplification involving *Kub3* and *Cdk4*, which suggest that these genes drive sarcomagenesis.

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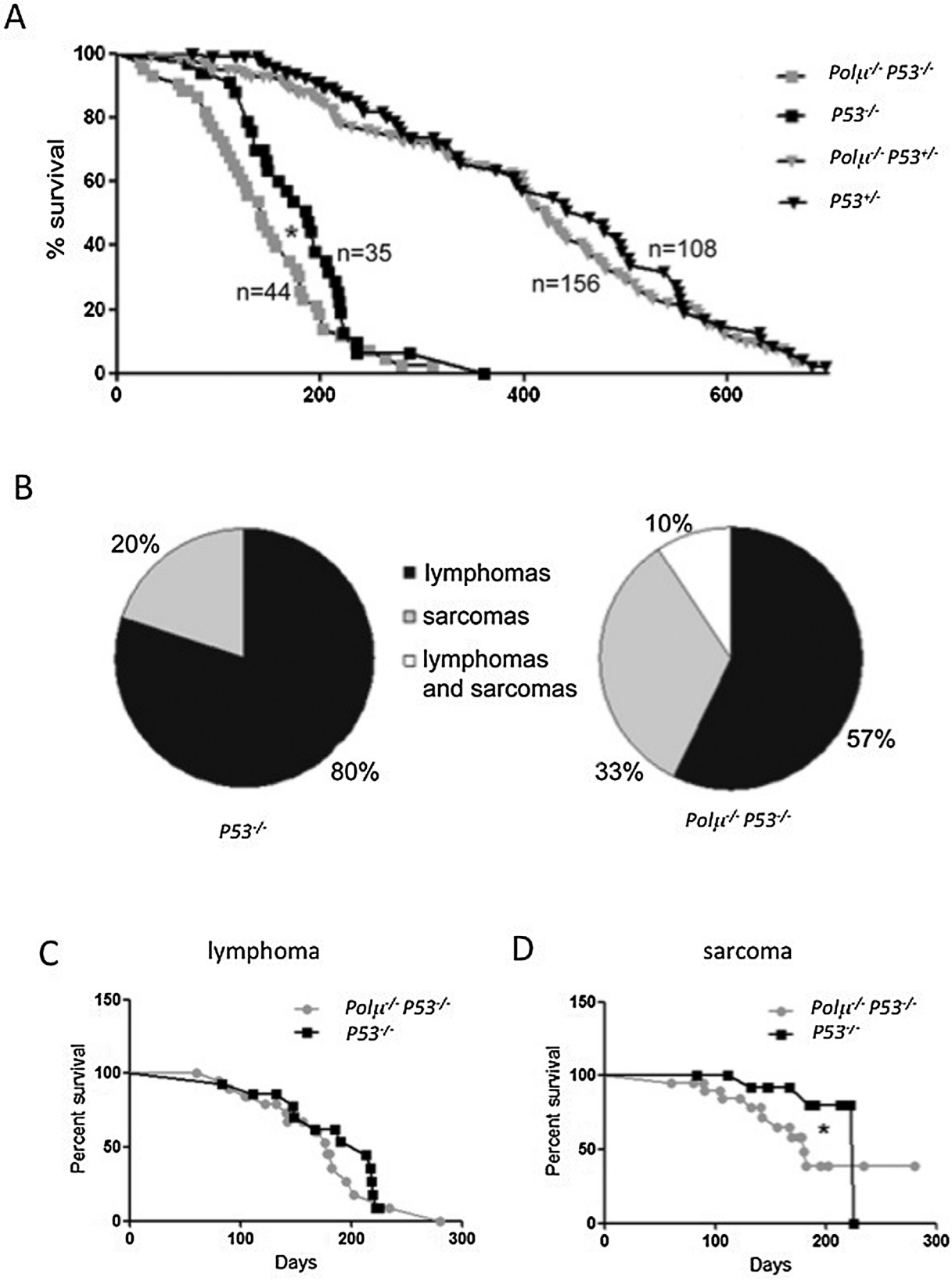

Fig. 1. *Polμ* deficiency effect on survival and tumor spectrum in $P53^{-/-}$ mice. A) Kaplan-Meier survival curve of various transgenic mice (*p = 0.04 log-rank test). B) Tumor spectrum in $P53^{-/-}$ and $Polμ^{-/-}P53^{-/-}$ mice (*p < 0.05 Chi-square test). C, D) Kaplan-Meier survival curve for $P53^{-/-}$ and $Polμ^{-/-}P53^{-/-}$ mice with lymphoma (C) or sarcoma (D) (*p = 0.04 log-rank test).