News & Views

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THE EMBO JOURNAL

Living a longer life: unique lessons from the naked mole-rat blood system

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Analysis of functional deterioration of the blood system during ageing has been largely confined to the mouse and human system. In this issue, Emmrich *et al* (2022) report the first comprehensive characterisation of the haematopoietic system of the naked mole-rat (NMR), an exceptionally long-lived rodent, highlighting its unique features and uncovering potential strategies to sustain haematopoiesis during an extended lifetime.

The EMBO Journal (2022) 41: e111759
See also: **S Emmrich *et al*** (August 2022)

Ageing is characterised by a progressive, time-dependent decline of body functions, accompanied by an increased risk of disease, which eventually leads to death. One of the key aspects of the ageing process is the progressive functional decline of somatic stem cells that lose their capacity to preserve tissue homeostasis as well as to maintain a functional pool of stem cells by self-renewal. In the long run, this contributes to stem cell exhaustion, diminished organ function and disease. The blood system is no exception to this, and the loss of haematopoietic stem cell (HSC) fitness accompanying old age manifests as an increased risk of malignancies, impaired response to infections and cytopenias, especially thymopenia and erythropenia (Geiger *et al*, 2013). Targeting the dysfunctions in the aged haematopoietic system has the potential to increase human health and lifespan, and direct interventions that ameliorate the ageing effects on HSCs hold great potential in this direction. In this issue of *EMBO Journal*, (Emmrich *et al*, 2022) explore the haematopoietic system of the naked mole-rat (NMR), a uniquely long-lived rodent, and report interesting evolutionary adaptations that might contribute to the longevity of this species.

In the haematopoietic ageing field, the great majority of studies have focussed so far on mice and, to some extent, humans. While the mouse model system offers many advantages, the use of other models can widen our understanding of ageing of the haematopoietic system and provide researchers with novel tools to target ageing in humans. Emmrich *et al* (2022) here present an elegant in-depth characterisation of the haematopoietic system of the NMR and offer a set of useful tools in the form of species cross-reactive antibodies for flow cytometric analysis, as well as a single-cell transcriptomic profiling database easily accessible using a dedicated online interface. Emmrich *et al* (2022) also uncover several novel features of NMR haematopoietic system that might have evolved to support their exceptionally long life (Fig 1). One of the striking examples in that respect is the fact that NMRs suffer no age-associated changes in the cell frequencies between different immune cell subtypes at least until middle age, a phenomenon that is evident in both mice and humans. Indeed, with increased age, both humans and mice exhibit a skewing towards myeloid cells, to the detriment of cells of the lymphoid lineage (Geiger *et al*, 2013). When comparing middle-aged NMR (11 years old) to their young adult counterparts (3 years old), the youthful peripheral blood composition was maintained into middle age in NMR, and gene expression profiling from single-cell transcriptomic data of haematopoietic stem and progenitor cells (HSPCs) from the bone marrow of middle-aged NMRs showed no myeloid differentiation bias, in contrast to humans and mice (Geiger *et al*, 2013). Instead, while the HSPC pool expanded slightly with age in NMRs, as also reflected in the gene set enrichment analysis of the transcriptomic data, NMR HSPCs upregulate pathways related to the detoxification of oxidants and DNA repair, which might serve to protect the stem cell compartment into old age. Furthermore, when analysing peripheral blood and bone marrow transcriptomic data from middle-aged compared with young NMRs using two different murine ageing clocks (Tyshkovskiy *et al*, 2019), there was no increase in median transcriptomic age in the NMR, contrary to the case in the murine equivalent age groups (3 vs. 12 months of age).

Moreover, the inflammatory phenotype that usually accompanies ageing, so-called "Inflammaging" (Fulop *et al*, 2021), was found to be absent at least up until middle age in the NMR and the single-cell transcriptomic profiling of HSPCs consistently showed that several inflammation-related pathways were negatively correlated with increasing age in the NMR. Interestingly, haematopoietic cells from NMRs proved to be also overall less responsive to inflammatory signals through the interferon type 1 signalling pathway, supported by the lack of inflammatory response after poly(I:C) treatment. Consistently, interferon α receptors (IFNAR1) were expressed at relatively low levels on both HSPCs and

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DOI 10.15252/embj.2022111759 | The EMBO Journal (2022) 41: e111759 | Published online 4 July 2022

immune effector cells such as granulocytes and macrophages. Emmrich *et al* (2022) hypothesise that this might be reflective of the low viral environment that the NMR has evolved in, which is further supported by the fact that NMRs are notoriously susceptible to viral infections (Artwohl *et al*, 2009).

Many of the issues that accompany ageing in the haematopoietic system trace directly to the HSC/HSPC compartment, which displays several intrinsic detrimental changes with increasing age. One key intrinsic aspect of HSCs in the human and murine bone marrow is their capacity to establish

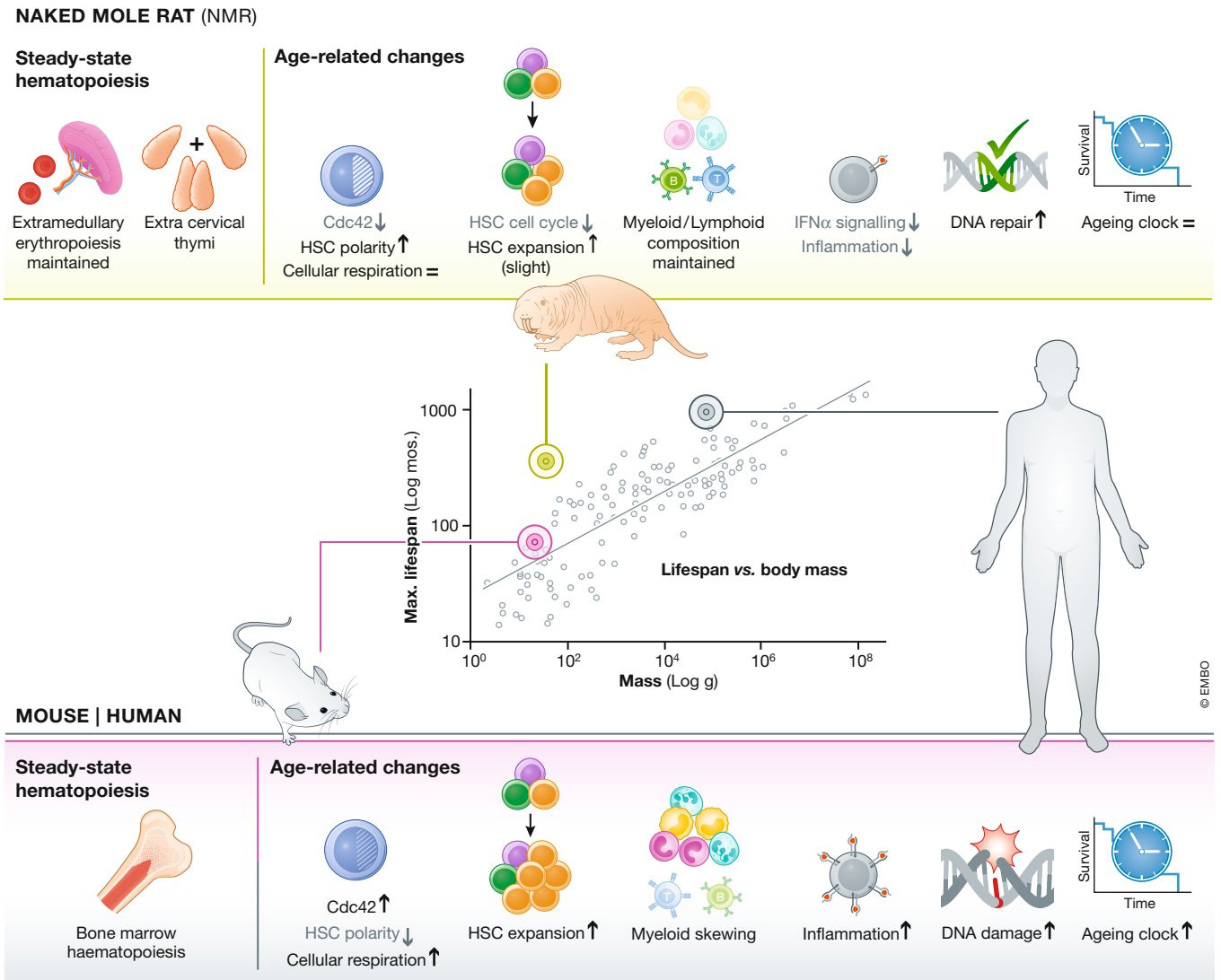

Figure 1. Differences in the haematopoietic system of the naked mole-rat (NMR) compared with mice and humans.
(Center): Maximum lifespan plotted against the average body mass of a random selection of nonvolant mammals (Ernest, 2003) with the datapoints for mice (red), NMR (green) and human (light grey) highlighted. NMRs show increased relative longevity compared with similar-sized mammals. Human and mice are on average also living longer than mammals with similar body size, but NMR is comparatively outperforming both human and mice. (Top): Characteristics of the NMR haematopoietic system potentially contributing to its longevity. NMRs maintain splenic erythropoiesis into adulthood as well as an extra set of cervical thymi. NMRs exhibit no myeloid skewing in their peripheral blood or in the transcriptomic profile of the haematopoietic stem progenitor cell (HSPC) compartment. Likewise, transcriptomic data reveal no age-related upregulation of inflammatory markers, but instead an upregulation of cytoprotective pathways. The transcriptomic profile of middle-aged NMR shows no increase in age markers as defined by ageing clocks. HSC/HSPC cells from NMRs retain their cellular polarity and have a low cellular metabolism and a very low expression of Cdc42. With age, the HSPC pool is mildly expanded in the NMR bone marrow, but the HSCs remain quiescent and have a comparatively increased cell cycle length. (Bottom): In contrast, mice and humans terminate their extramedullary haematopoiesis after the neonatal period. HSCs lose their cellular polarity, and the systemic and local production of Cdc42 increases with age. Mouse HSCs have a high metabolic rate compared with the NMR and human, but both human and mice HSCs have an increased metabolic rate with age. Both humans and mice gain inflammatory markers with age, and their transcriptomic profiles show increased age markers as scored by ageing clocks. The peripheral blood compartment shows a myeloid skewing with increased age, and no cytoprotective pathways are upregulated in the HSPC compartment with age. The HSC compartment also expands with age in a clonal manner.

cell polarity, which is lost in advanced age (Mejia-Ramirez *et al,* 2021). The key polarity regulator Cdc42 shows itself a polar distribution directly linked to murine and human HSC fitness (Geiger *et al,* 2013; Amoah *et al,* 2022), and a progressive increase in Cdc42 activity level contributes to ageing of the haematopoietic system. Interestingly, Emmrich *et al* (2022) show that Cdc42 is not polar in the NMR HSPC compartment and Cdc42 is expressed to an overall extremely low level in these cells, which might prevent Cdc42 over-activation with ageing. Noteworthy, the cytoskeletal protein tubulin was showing a polar distribution that was maintained into middle-aged NMR stem cells, while murine HSPCs lose both Cdc42 and tubulin polarity in a comparative timeframe. Another key aspect of human and murine HSCs is their low metabolic rate, which was confirmed to be a shared characteristic of NMRs. Here, HSPCs from NMRs more closely resembled human HSCs and relied more heavily on oxidative phosphorylation compared with murine HSCs. NMRs also demonstrated a protective measurement against the aldehydes produced through lipid peroxidation in the fatty acid oxidation pathways enriched in NMRs, in the form of elevated levels of aldehyde dehydrogenases. In addition, the authors reported that the most stem cell-like compartment of NMR HSPCs, termed the LTC (lineage negative, Thyr1.1 and CD34-positive cells) compartment, contains a higher fraction of quiescent cells compared with the HSC compartment from mice, and all haematopoietic cells from the NMR have a longer cell cycle compared with murine cells. A comparatively low metabolic profile rate, coupled with slow cell cycling of HSPCs, is likely a contributing factor to the longevity of the NMR.

While adult mammal haematopoiesis usually is confined to the bone marrow, foetal and neonatal haematopoiesis often takes place within secondary organs, such as the spleen. Interestingly, Emmrich *et al* (2022) demonstrated that NMRs maintain splenic erythropoiesis into the adult stage of their life, which can be considered a neotenic trait. Neoteny has been linked to longevity before by others, and NMRs and humans have both been suggested to be neotenic species of their respective mammalian orders (Skulachev *et al,* 2017). Apart from being a neotenic trait, splenic erythropoiesis was theorised to contribute to the maintenance of erythropoiesis into middle age in the NMR and might prevent age-related anaemia by supporting red blood cell production throughout life.

The peripheral blood composition in NMRs is overall skewed towards the myeloid cell lineages, which has been previously hypothesised to support their long life (Hilton *et al,* 2019). The NMRs have a comparatively large granulocytic and erythrocytic compartment compared with both humans and mice but show a reduction in the B-cell compartment. Interestingly, they also have a T-cell profile that shows an enrichment of $CD4^+$ cells over $CD8^+$ cells, suggesting that NMRs have a reduced cell-mediated immunity, which is further strengthened by the fact that NMRs lack natural killer T-cells (Hilton *et al,* 2019). The increase in mature $CD4^+$ T-cells together with the smaller B-cell compartment could mean that antigen-presentation from CD4-to-B-cells is more effective in NMRs compared with other mammals.

The absence of many age-related phenotypes of the murine and human HSPC compartment in the NMR makes this small rodent unique, further supporting its relevance for ageing studies. While many of the features of the NMR haematopoietic system are likely the result of adaptations to a highly unique environment, they have the potential to provide clues on how to maintain a long lifespan that translates into the human setting. Questions arise, however, regarding some of the clinically relevant phenotypes not investigated by Emmrich *et al* (2022) in the NMR, such as Clonal Haematopoiesis of Indeterminate Potential (CHIP). If the NMRs also lack this age-related phenotype, coupled with the absence of both increased systemic inflammation and myeloid skewing, they could serve as a blueprint for investigating how to lessen the impact of these conditions in humans. This generates interesting questions into how the NMR maintains such rigid control over the HSPC lineage output with ageing to avoid myeloid skewing of its already myeloid-prone haematopoietic system, and how inflammatory processes might be restrained over time.

Another interesting aspect of the ageing NMR haematopoietic system is the ability to maintain HSC fitness into middle age. Especially, the capacity of HSCs to maintain polarity and quiescence with increased age is quite intriguing and warrants complementary analysis. Since the cell polarity regulator Cdc42 is expressed at such a low level in NMR HSCs and is itself not polarly distributed, the pathway to establishment and maintenance of HSPC polarity is still not understood in these animals.

In conclusion, the use of alternative models to study ageing holds great potential for the ageing field, and this study by Emmrich *et al* (2022) has not only provided the research community with a set of useful research tools, but it has also revealed exciting insights into unique strategies to maintain a healthy immune system with ageing and ultimately possibly achieve a longer life (Fig 1).

Disclosure and competing interests statement

The authors declare that they have no conflict of interest.

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