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Our life companions: the human follicular mite *Demodex folliculorum**

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We carry them in our skin pores through our entire life, from birth to death. We offer them shelter and in return, they tidy-up our pores. We go on with our busy day life and they sleep. They wake up when we go to sleep and while we are deeply dreaming, they move around, visit other pores and mates, and reproduce. Despite being our 'very own' life companions, until recently, we knew very little about their struggle.

Their miniaturised Bauplan is perfectly fit for life inside the pores of hair follicles and sebaceous glands. Perception of light is achieved by one of the smallest 'eyes' (photoreceptors) known to date, and movement and dispersal is accomplished by minute legs powered by just three unicellular-uninucleate muscle segments. With a unique arrangement of *Hox* genes, their reproductive organs allow them to mate and to deliver offspring inside the limited space offered by the pores.

Unless they soon find a way out, genome erosion, on an evolutionary time scale, is leading them to a dead end, to extinction. They outbreed less and less: each of us has a unique population, started by a few colonisers, legacy of our moms when we were babies. This resulted in a mite species that presents the lowest number of protein genes. Yet, they manage to successfully carry on with their lives by synchronising with our lifestyles, and we hope they will keep doing it for the foreseeable future!

Demodex folliculorum (Prostigmata, Demodecidae) has adapted to the life in the human pores and the circadian rhythm of their host (Smith *et al.*, 2022). The difference between an ectosymbiont and a pathogen lies in the numbers. The amount of *Demodex* mites on healthy human faces is controlled by several factors.

First, the physical size of the pores. The older a person gets, the wider the pores become and the more mites a pore can accommodate (Zeytun, 2017; El Bassiouni *et al.*, 2005). Pore size also increases with inflammation and with it *Demodex* (Casas *et al*., 2012; Karabay and Çerman, 2020; Forton and De Maertelaer, 2021).

Second, the physiology, the feeding of the mites. The mites feed on sebum produced inside the pores. Sebum production is the highest in the age range of 20 to 30 years (Foley *et al.*, 2021).

The immune system of a healthy person seems to control the density of *Demodex*. This becomes evident in various ways.

Suppression of cellular immunity by cancers might lead to increase in *Demodex* numbers or to abnormal antiparasitic attacks of the immune system on *Demodex* (Seyhan *et al.*, 2004; Bakacak *et al*., 2020; Ziaja-Sołtys *et al*., 2021). Immunosuppressive viruses such as HIV I can lead to an increase of *Demodex* (Yamaoka *et al.*, 2014; Grigoryan *et al*., 2018; Trama *et al.*, 2018). Iatrogenic induced immunosuppression for the treatment of autoimmune diseases, essential thrombocytosis, Crohn's disease, psoriasis, Cushing's syndrome and neoplasms, and for the support of organ transplantation support demodicosis/demodicidosis (Amitay-Laish *et al*., 2022). Autoimmune diseases themselves in the form of failure of the thyroid in humans and dogs or in rheumatoid arthritis can lead to breakdown of the host's regulation of *Demodex* density (Pinsenschaum *et al*., 2019; Yazisiz *et al.*, 2020; Dursun *et al.*, 2022). From alcoholism to heart failure, if homeostasis is compromised, *Demodex* increases (Kokaçya *et al.*, 2016; Yüksel and Yüksel, 2020; Pormann *et al.*, 2021). This are all cases of secondary demodicosis.

The older clinical literature on demodicosis in humans and dogs argues that *Demodex* suppresses the host

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immune system and therefore leads to the clinical manifestations. These reports fail to explain why or how *Demodex* persists in healthy humans and dogs.

Bit by bit, mechanisms of immune dysregulation are being discovered that lead to pathological levels of *Demodex*. Paediatric demodicosis, chronic demodicosis, and demodicosis as part of rosacea in humans is caused by a *Signal transducer and activator of transcription (STAT) 1* heterozygous gain-of-function (GOF) mutations eventually leading to excessive interferon γ response and compromised T helper cell 17 differentiation (Second *et al.*, 2017; Molho-Pessach *et al.*, 2020; Saez-de-Ocariz *et al.*, 2020; Baghad *et al.*, 2021; Martinot *et al.*, 2021; Shamriz *et al.*, 2021; Zhang *et al.*, 2021).

Demodex is controlled by its host through innate type 2 immunity (Ricardo-Gonzalez *et al.*, 2022). This raises the question whether primary demodicosis in humans exists at all.

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