

Correspondence

A tribute to eosinophils from a comparative and evolutionary perspective

To the Editor:

Eosinophils have distinctive morphological and biochemical features differentiating them from other granulocytes. Fig 1 shows eosinophils in vertebrates across taxa from an evolutionary perspective, demonstrating an appreciation of their morphological diversity despite a number of conserved features that define the lineage. The presence of “eosinophilic” or acidophilic blood cells/hemocytes has been recognized as well in various invertebrate species, but it is still unknown whether these are evolutionary precursors to eosinophils in vertebrates.¹ Notably, coelacanth, estimated to have evolved 350 million years ago, already had eosinophils.² There is evidence that neutrophil and eosinophil myeloperoxidase diverged approximately 60 to 70 million years ago, well before mammalian species, suggesting specialization of this unique granulocyte type.¹

As evident from Fig 1, eosinophils vary most particularly in the size and appearance of their eosin-stained secondary (specific) granules, for example, the very large granules seen in the crocodile, tortoise, and horse, compared with most other taxa represented here. As well, there is considerable conservation of nuclear morphology, particularly the presence of a segmented nucleus in most of these taxa; reptiles consistently have nonsegmented nuclei, and amphibians appear to have segmented or round nuclei, although the significance of this nuclear morphology remains to be determined.

The “LIAR” (Local Immunity And/or Remodeling/Repair) hypothesis, derived principally from mouse models, expanded understanding of eosinophils beyond end-stage effector cells involved in host defense against parasites and other pathogens.³ In fact, eosinophils or eosinophilic granule-containing hemocytes are crucial in tissue remodeling including involvement in metamorphosis in amphibians and invertebrates, respectively, demonstrating their participation in concerted events in pathways of developmental biology and metabolism, modulation of innate and adaptive immune responses, maintenance of tissue and metabolic homeostasis, and involvement in tissue remodeling and fibrosis in human disease pathogenesis.^{1,3} However, these findings are contrasted by transgenic mouse models in which the eosinophil lineage was eliminated, but surprisingly no significant clinical abnormalities have been evident in these animals under specific pathogen-free vivarium conditions.¹ Given their involvement in complex physiological processes, the question of the eosinophils’ continuous involvement in ongoing evolutionary processes across taxa seems logical and intriguing.^{1,4}

In human medicine, eosinophils are a focus of targeted therapeutics and basic investigations, including functions in

tissue homeostasis in health and roles in disease. In contrast to the mouse, eosinophil-targeting biologics that partially or more fully deplete eosinophils have thus far proven safe across a range of eosinophilic inflammatory disorders, with no evidence of increased infections, malignancies, or other pathological conditions, for example, in patients with asthma and hypereosinophilic syndrome (HES) treated with anti-IL-5 for up to approximately 5 years.⁴ The NIH Taskforce on the Research of Eosinophil-Associated Diseases (TREAD), recently updated to “RE-TREAD,” identified multidisciplinary priority areas setting the stage for future research efforts, with the ultimate goal to develop novel diagnostic and advanced molecular-level therapeutic strategies for eosinophil-associated diseases in humans.⁵

In the animal kingdom, most knowledge of eosinophil biology is derived from mouse models and human studies, and more recently zebrafish. Basic research has elucidated a comparatively limited understanding of eosinophil kinetics and functions in health, during physiological alterations, and in disease pathogenesis in nonhuman vertebrate species. Eosinophil involvement in allergy and hypersensitivity are well described in clinical conditions in domestic species, most commonly with asthma in dogs and cats, allergies (mainly to food or insect bites), and HES described in cats, dogs, and horses. As in humans, molecular and genetic techniques are needed to differentiate HES and eosinophil leukemia. These considerations highlight a research area in need of attention to benefit our understanding of evolutionary aspects through translational research, ultimately advancing the comparative perspective to improve diagnostic capacities and ultimately treatment strategies across taxa.

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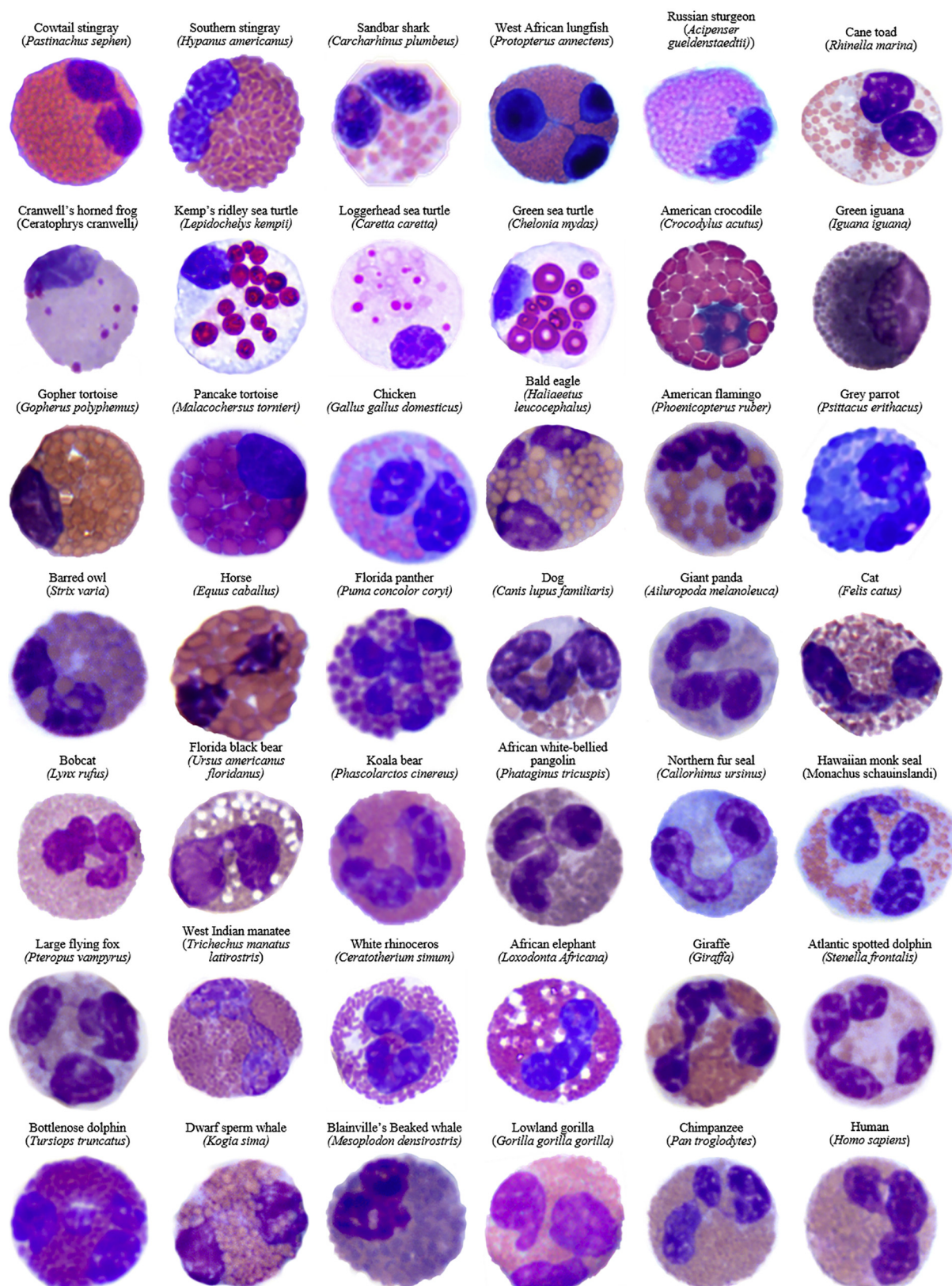


FIG 1. Image composite showing the morphology of eosinophils from representatives across vertebrate taxa from an evolutionary perspective, starting with fish, amphibians, reptiles, birds, mammals, to human, showing a considerable amount of consistency as well as morphological variability as recognized by light microscopy. Wright-Giemsa stain. $\times 100$ objective.