Animal Models of Human Granulocyte Diseases

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KEYWORDS

• Chronic granulomatous disease • Leukocyte adhesion deficiency
• Severe congenital neutropenia • Neutrophils • Mouse models • Zebrafish models

KEY POINTS

- Human granulocyte diseases are mostly monogenic diseases affecting neutrophils, not eosinophils and basophils.
- Most monogenic neutrophil diseases are recessive or X-linked and can be classified as chronic granulomatous disease (CGD), leukocyte adhesion deficiency (LAD), or severe congenital neutropenia (SCN). Each of these can be caused by mutations in different genes.
- For CGD and LAD, mice bred to lack the orthologous gene mutated in each human form usually have a phenotype similar to that of the human patients. In contrast, for SCN, there is a striking discrepancy between the phenotypes of model mice and human patients.
- Not all animal models are mouse models. For some neutrophil diseases, there are naturally occurring models in dogs or cows. The construction of zebrafish models is an emerging trend in neutrophil diseases.
- Opportunities to characterize new monogenic forms of SCN, to generate new mouse models by random mutagenesis, to engineer new zebrafish models, and to use animal models in the exploration of new treatments should occupy researchers studying animal models of neutrophil diseases for many years to come.

INTRODUCTION

Granulocytes are immune cells that contain within them punctate granules, visible under the light microscope. There are 3 categories of granulocytes: basophils, neutrophils, and eosinophils, that are distinguished by whether they can be usefully stained by

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basic (high pH), neutral (medium pH), or acidic (low pH) stains. Eosinophils may have several roles in host defense and have been most widely studied in asthma.[1] Both eosinophils and basophils have roles in promoting the Th2 responses needed to defend against parasitic infections.[1,2] However, a search of OMIM (Online Mendelian Inheritance in Man) shows no monogenic disorders primarily attributed to eosinophil or basophil dysfunction. By laboratory assays, humans have been found with a partial or total lack of peroxidase in eosinophil granules, but they have mild anemia or no phenotype at all.[3] Ohnmacht and colleagues[4] generated mice lacking basophils, which will enable targeted studies of human diseases in which basophils may be important. The immune function of neutrophils and their roles in disease are much better characterized than those of basophils and eosinophils, so neutrophils and their diseases are focused on entirely in this article.

Neutrophils are first responders at sites of infection and part of the innate immune system. Neutrophils can fight an infection by diverse weapons: phagocytosis of the infecting microbe,[5] poisoning the microbe with toxic peptides stored in the granules,[6] and wrapping the microbe in neutrophil extracellular traps.[7] More generally, neutrophils enhance inflammation and inflammatory signals that eventually call in macrophages, T cells, and B cells for a more long-lasting attack on the infection. Consistent with the paradigm that the innate immune system is more primitive than the adaptive immune system, all jawed vertebrates are thought to have neutrophils or neutrophil-like cells called heterophils, which can kill microbes by phagocytosis.[8,9] Even some invertebrates, such as flies, have neutrophil-like cells.[10] One reason eosinophils are thought be important for parasitic infections is that parasites, such as helminths, are too large to be killed by phagocytosis.[1]

Not only are neutrophils conserved across jawed vertebrates, but so are most of the known genes mutated in human neutrophil diseases. This evolutionary perspective suggests that it might be possible to model each human neutrophil disease of known monogenic cause by knocking out the corresponding gene in a mouse and characterizing the mouse phenotype. One could also hope to discover new human diseases by first studying abnormal mice that turn out to have a neutrophil disease. In a few cases, fish have been deliberately used instead of mice; also included are naturally occurring models of 2 diseases in dogs and 1 disease in cows.

Classification of Neutrophil Diseases

Most human monogenic neutrophil diseases can be classified according to the type of malfunction. Conditions in which neutrophil defense is inadequate because the number of circulating neutrophils are too low, as measured by the absolute neutrophil count (ANC), are called neutropenia. Chronic benign and ethnic neutropenias are not discussed, but the focus instead is on neutropenias that may start at birth and that are associated with severe bacterial infections, called severe congenital neutropenia (SCN). Diseases in which neutrophils fail to migrate properly to sites of infection are called leukocyte adhesion deficiency (LAD). Diseases in which neutrophils fail to carry out the oxidative burst function are called chronic granulomatous disease (CGD). Based on these layman's descriptions, one might imagine that SCN would be easiest to explain at a molecular level and CGD would be the hardest to explain at a molecular level; the causes of neutropenia would be most conserved across species and the causes of CGD least conserved across species. Surprisingly, the opposite is true for both measures of complexity. Therefore, relevant animal models are presented in the following order: CGD, then LAD, then SCN, from best understood to least understood. One rare disease, due a mutation in *RAC2*, is at the boundary of CGD and LAD and that disease is described in the LAD section. Two monogenic diseases that do not