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Review Article

Immunotoxic effects of environmental pollutants in marine mammals

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ABSTRACT

Due to their marine ecology and life-history, marine mammals accumulate some of the highest levels of environmental contaminants of all wildlife. Given the increasing prevalence and severity of diseases in marine wildlife, it is imperative to understand how pollutants affect the immune system and consequently disease susceptibility. Advancements and adaptations of analytical techniques have facilitated marine mammal immunotoxicology research. Field studies, captive-feeding experiments and in vitro laboratory studies with marine mammals have associated exposure to environmental pollutants, most notable polychlorinated biphenyls (PCBs), organochlorine pesticides and heavy metals, to alterations of both the innate and adaptive arms of immune systems, which include aspects of cellular and humoral immunity. For marine mammals, reported immunotoxicology endpoints fell into several major categories: immune tissue histopathology, haematology/circulating immune cell populations, functional immune assays (lymphocyte proliferation, phagocytosis, respiratory burst, and natural killer cell activity), immunoglobulin production, and cytokine gene expression. Lymphocyte proliferation is by far the most commonly used immune assay, with studies using different organic pollutants and metals predominantly reporting immunosuppressive effects despite the many differences in study design and animal life history. Using combined field and laboratory data, we determined effect threshold levels for suppression of lymphocyte proliferation to be between <0.001–10 ppm for PCBs, 0.002–1.3 ppm for Hg, 0.009–0.06 for MeHg, and 0.1–2.4 for cadmium in polar bears and several pinniped and cetacean species. Similarly, thresholds for suppression of phagocytosis were 0.6–1.4 and 0.08–1.9 ppm for PCBs and mercury, respectively. Although data are lacking for many important immune endpoints and mechanisms of specific immune alterations are not well understood, this review revealed a systemic suppression of immune function in marine mammals exposed to environmental contaminants. Exposure to immunotoxic contaminants may have significant population level consequences as a contributing factor to increasing anthropogenic stress in wildlife and infectious disease outbreaks.

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1. Introduction

1.1. Immunotoxicology and risk assessment

The field of toxicology grew due to concerns about adverse effects of chemical substances on humans, then gradual attention was given to domestic animals and wildlife (Newman and Unger, 2003). Traditional toxicity assessments focused on endpoints relating to morbidity or mortality, but it was not until the 1970s that specific interactions of xenobiotics with elements of the immune system were discovered. The first review of immunotoxicology by Vos (1977) was fundamental in establishing that exposure to a broad spectrum of xenobiotics can alter lymphoid tissues and cell populations as well as the function of immune responses, subsequently affecting the health of exposed animals. The immunotoxicity of chemicals can now be assessed via their effects in three broad categories: histopathology of lymphoid tissues, changes in immune function and/or frequency and characteristics of immune cell populations, and changes in host resistance to infectious pathogens (Kimber and Dearman, 2002). In a comprehensive study of the immunotoxicity of over 50 chemicals in mice (*Mus musculus*), the U.S. National Toxicology Program (NTP) established strong correlations between changes in a battery of immune endpoints and altered host resistance (Luster et al., 1992, 1993). These results confirmed the utility and sensitivity of immune endpoints as indicators of toxic insult.

Knowledge of the nature and magnitude of potential adverse health risks from exposure to immunotoxic contaminants is invaluable for the generation of management or conservation plans in highly exposed populations. The assessment of risk combines exposure and relevant dose–response data to estimate the potential of adverse effects (Luster et al., 1994), and while much information is available on exposure and tissue levels of contaminants in marine mammals and other wildlife, dose–response data are lacking, particularly for immunotoxicity. Establishment of threshold effect levels, lowest observable effect levels and/or EC50 for various contaminants are needed for relevant immune endpoints in order to assess potential hazards. These are often difficult to establish for marine mammals due to ethical and logistical constraints related to field and experimental work. Furthermore, there is additional need and challenges to extrapolate effects at the molecular, cellular and individual level to the population level, which is most relevant for management and conservation.

1.2. The marine mammal immune system

The ultimate function of the immune system is to protect against infectious diseases, which may be caused by invading parasites, viruses, bacteria or other microorganisms, and also to respond to aberrant macromolecules such as cancerous cells (Abbas et al., 2012). The immune system is comprised of a complex network of tissues, cells and molecules that work in a concerted effort to resist infections (Fig.ure 1). The immune response to invading pathogens consists of two separate, but interconnected functional systems: innate/non-specific immunity and adaptive/specific immunity; the most important difference between the arms of the immune system is the specificity and memory response of adaptive immunity. Together, the innate and adaptive arms provide immediate and long-term protection from infectious pathogens.

Research over the decades has revealed few differences between the immune system of marine and more highly studied terrestrial mammals, such that much of our understanding of marine mammals comes from rodent and human immunology. The innate immune system consists of various cells and biochemical mechanisms in place to protect the host within minutes and hours of exposure to antigenic stimuli (Fig. 1). Immune cells in marine mammals have been characterized using cross-reactive and species specific monoclonal and polyclonal antibodies against cell surface antigens, including various Cluster of Differentiation (CD) markers, major histocompatibility complex (MHC), and other surface proteins (De Guise, 2004; Ross and De Guise, 2007). Phagocytic cells involved in the rapid destruction of invading pathogens, such as neutrophils, macrophages and dendritic cells, were characterized first in several cetacean species (De Guise et al., 2004; Jaber et al., 2003a,b; Kawashima et al., 2004) and quantitative assays to measure phagocyte function were also developed (De Guise et al., 1995a; Noda et al., 2003). The function of natural killer (NK) cells, specialized lymphocytes involved in the killing of virus infected and tumour cells, has been described in harbour seals (Ross et al.,

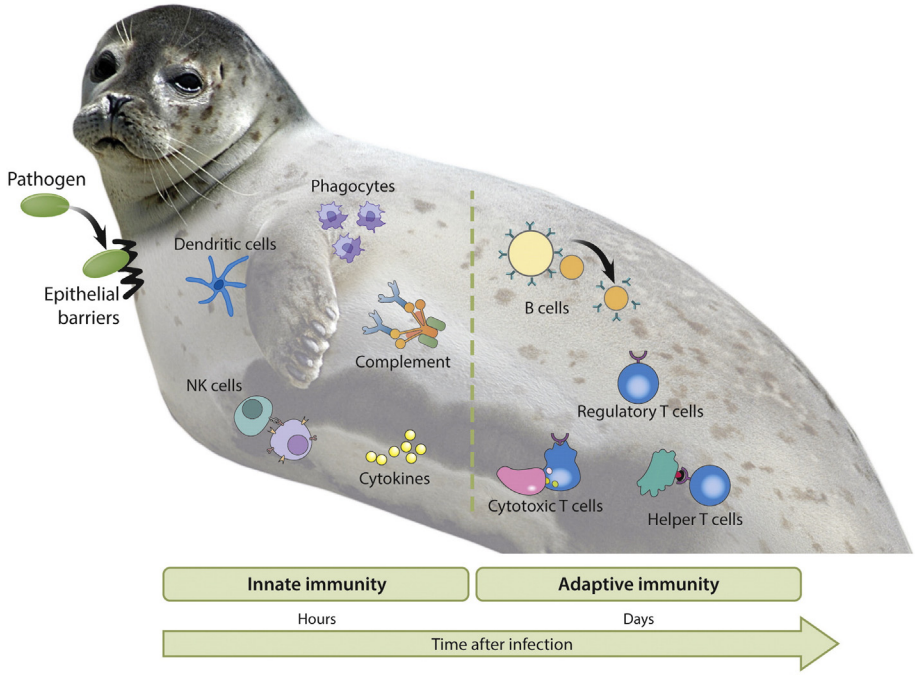

Fig. 1. Cells and molecules of the mammalian innate and adaptive immune system. The function of the immune system is to combat invading pathogens or cancerous cells and this functionality relies on the interaction of a number of innate and adaptive cells and secreted proteins.