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Review

The translational value of non-human primates in preclinical research on infection and immunopathology

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ABSTRACT

The immune system plays a central role in the defense against environmental threats – such as infection with viruses, parasites or bacteria – but can also be a cause of disease, such as in the case of allergic or autoimmune disorders. In the past decades the impressive development of biotechnology has provided scientists with biological tools for the development of highly selective treatments for the different types of disorders. However, despite some clear successes the translation of scientific discoveries into effective treatments has remained challenging. The often-disappointing predictive validity of the preclinical animal models that are used in the selection of the most promising vaccine or drug candidates is the Achilles heel in the therapy development process. This publication summarizes the relevance and usage of non-human primates as pre-clinical model in infectious and autoimmune diseases, in particular for biologicals, which due to their high species-specificity are inactive in lower species.

Contents

Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; AID, autoimmune disease; AIDS, acquired immunodeficiency syndrome; AMA-1, apical membrane antigen-1; APC, antigen presenting cell; ATG, anti-thymocyte globuline; BCG, Bacille Calmette-Guérin; BPRC, Biomedical Primate Research Centre; CalHV3, Callithrix herpesvirus-3; CD, cluster of differentiation; CDC, complement-dependent cytotoxicity; CFA, complete Freund adjuvant; CIA, collagen-induced arthritis; CMV, cytomegalovirus; CT, computed tomography; CTL, cytotoxic T lymphocyte; DF, dengue fever; DNA, desoxyribonucleic acid; DV, Dengue virus; EAE, experimental autoimmune encephalomyelitis; EBV, Epstein Barr Virus; FIV, feline immunodeficiency virus; Flu, influenza; GWAS, Genome-wide association studies; HIV, human immunodeficiency virus; IDO, indole-amine 2,3-dioxygenase; IFA, incomplete Freund adjuvant; IFN, interferon; Ig, immunoglobulin; mHAg, minor histocompatibility antigens; mAb, monoclonal antibody; MHC, major histocompatibility complex; MOG, myelin oligodendrocyte glycoprotein; MS, multiple sclerosis; MSP, merozoite-specific protein; M.tb, *Mycobacterium tuberculosis*; NHP, non-human primates; NK, natural killer; NNRTIs, non-nucleoside reverse-transcriptase inhibitors; ORF, open reading frame; PBMC, peripheral blood mononuclear cells; RA, rheumatoid arthritis; PET, positron emission tomography; RT, reverse transcriptase; R&D, research and development; SIV, simian immunodeficiency virus; SHIV, simian human immunodeficiency viruses; SPF, specific pathogen free; TB, tuberculosis; TCR, T cell (antigen) receptor; Th, T helper; TLR, Toll-like receptor; Tmem, memory T cells; TNF, tumor necrosis factor; WNV, West Nile virus

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1. Introduction

The immune system plays a central role in the maintenance of homeostasis in the human body. The system executes this task at multiple levels, such as by passive and active protection against the invasion of exogenous micro-organisms, by containment of endogenous micro-organisms that cause chronic latent infections (e.g. herpes- or polyomaviruses), the suppression of cancer, by limiting reactions against tissue injury and by the stimulation of tissue repair. Failure to properly execute this multi-faceted task can lead to pathology and disease. Disturbance of homeostasis can be caused by an unwanted excessive immune reaction, such as in autoimmunity and the rejection of a transplanted organ or by an insufficient response of the immune system, such as in infectious diseases.

The impressive developments in the field of biotechnology have given scientists a plethora of tools for developing safe and highly specific biological agents with which the immune system can be helped to restore homeostasis when disturbed. A parallel development has been the generation of animal disease models, which can be used for the identification of potential targets of therapeutic agents and for their safety and efficacy evaluation. However, translation of scientific discoveries into effective treatments has been notoriously difficult. This causes the frustrating and highly cost-ineffective situation that in some disease areas $>90\%$ of promising new treatments failed in clinical trials (Kola and Landis, 2004).

The reasons of the high attrition rate seem to be diverse:

1. the targeted pathogenic process can be differently expressed in the animal model than in the patient,
2. the therapeutic entity or its formulation with immune potentiating agents (adjuvants), such as in vaccines, can have unacceptable side-effects,
3. the therapeutic entity can elicit a neutralizing response and is inactivated before it can exert its beneficial activities.

Apparently, essential links are missing between animal models currently used in preclinical research and the patient. This seems to hamper smooth translation of promising treatments from lab to clinic.

2. Animal models in immunology research

While in earlier days of immunology a diversity of species was used, nowadays preclinical research focuses on a limited number of inbred/SPF mouse strains. Reasons are the low costs, the high reproducibility due to lack of genetic variation within strains and the wide availability of reagents and genetically-modified strains. This may explain that also the currently used immunological disease models are based on a limited number of disease models, C57BL6 in particular.

Although the importance of the mouse as animal disease model for the dissection of immunopathogenic mechanisms can hardly be overestimated, its general validity for immunotherapy development seems to be hampered by fundamental immunobiological differences between a young inbred SPF mouse and an adult human patient (Mestas and Hughes, 2004). In this review we will discuss that important new insights lessons can be gained from disease models in species more closely related to humans, the non-human primates (NHP) in particular. While discussing how such models can help bridge the wide gap between commonly used rodent disease models and the patient, we will also pay special attention to the 3R principles, i.e. the refinement, replacement and reduction of animal research.

3. General considerations on the non-human primate as immunological model

The mouse has been an essential and powerful research tool in almost all discoveries made in the past 30 years regarding the role of the immune system in health and disease. However, increasing difficulties encountered in the translation of these discoveries into effective therapies for immune-based diseases raise the question to what extent pathogenic and therapeutic principles developed in laboratory mice can be extrapolated to the human immune system (Davis, 2008; Steinman and Mellman, 2004).

There are clear and well-established fundamental immunological differences between the innate as well as the adaptive arms of the human and mouse immune system (Davis, 2008; Mestas and Hughes, 2004). The closer similarity between NHP and humans is probably best illustrated at the level of the immunological synapse, a multi-molecular structure that is formed when immune cells interact, such as antigen-presenting cells (dendritic cells, B cells) with T cells or a cytotoxic T cell with a virus-infected target cell (Fig. 1). Essential components of the immunological synapse are as follows: i) the three molecular complex formed by an MHC molecule with antigenic peptide in its binding pocket in cognate interaction with the T cell antigen receptor (signal 1), ii) co-receptor molecules (CD4, CD8), iii) sets of co-stimulatory molecules that regulate the fate of the immune reaction (signal 2 via interaction of CD40&CD40L, OX40&OX40L, CD80/86&CD28, CTLA-4&CD28), and iv) adhesion molecules that stabilize cellular interactions (ICAM-1/LFA-1, LFA-3/CD2). The observation that matching combinations between APC and T cells from humans and rhesus monkeys can be found in which functional cross-talk can take place ('t Hart et al., 1997; Geluk et al., 1993) shows that even highly variable synaptic elements, such as MHC and TCR, can be evolutionary conserved.

Another important difference between humans and inbred/SPF mice is that the latter lack the strong influence of genetic diversity and life-long exposure to environmental pathogens on their immune system. Although we still have only superficial understanding of the influence on the immune system by the bacteria that populate our