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Beiträge der Veterinärmedizin zur biomedizinischen Grundlagenforschung

Die Veterinärmedizin ist in vielerlei Hinsicht eine sehr angewandte Wissenschaft, zugleich aber auch eine Disziplin, die wesentliche Beiträge zur biomedizinischen Grundlagenforschung liefert. Das breite Spektrum an Tier- und Krankheitsmodellen, mit denen die Veterinärmedizin arbeitet, eröffnet vielfältige Möglichkeiten für grundlegende Beiträge, beispielsweise zu Fragestellungen der Immunologie, zur Krebsentstehung und -therapie, zur Pharmakologie und Toxikologie oder zu der genetischen Basis von Krankheiten. Diese Beispiele werden in den nachfolgenden Beiträgen näher vorgestellt. Dabei ist es ein wichtiges Anliegen der Veterinärmedizin, die Grundlagenerkenntnisse in die praktische Anwendung zu überführen. Dadurch, dass die Veterinärmedizin sowohl Institute mit Schwerpunkten in der Grundlagenforschung beheimatet – wie im Folgenden am Beispiel des Instituts für Veterinärbiochemie und Molekularbiologie dargestellt – wie auch Institute mit Fokus auf der klinischen und diagnostischen Anwendung, bestehen beste Voraussetzungen, um tatsächlich den Schritt «from bench to bedside» zu machen, wie es im Folgenden am Beispiel der Veterinärdermatologie aufgezeigt wird.

The Importance of Veterinary Immunology

Artur Summerfield*, Giuseppe Bertoni, Kenneth McCullough*****

Immunology is a key discipline in veterinary medicine. By definition veterinary immunology is the science of the immune system of all animals which are in the focus of veterinary sciences and medicine. These typically include livestock, poultry, and fish species that are major food animals as well as companion animals such as cats, dogs, horses and rather exotic species for instance, rats, ferrets, camels and even reptiles. Furthermore, the immune system of wildlife species that act as reservoirs for food, companion or human infectious diseases may be included. The interest in some of these animals as models for human disease has received growing interest in recent years. Indeed, due to their size and resemblance to human physiology, large animals can be a valid and potentially superior alternative to the dominant murine immunology, which plays a pivotal role to unravel the basic principles of the immune system.

1. The immune system

The immune system has evolved to defend multicellular organisms against infections with viruses, bacteria or parasites which cause disease. Indeed, animals deprived of a fully functional immune system eventually succumb to the constant threat of harmful microorganisms. The capacity of the immune system to prevent such attacks is tightly connected to its ability to differentiate self and non-self, a feature which is crucial to avoid destruction of the own organism. In recent years, a different aspect of the immune system has become more and more prominent. This is the ability of the immune system to ignore or tolerate the multitude of harmless and essential microorganism which colonized the gastrointestinal tract, the genital tract, the airways and the skin. Based on these principle functions, the immune system is centrally implicated in many aspects of health and well-being of animals and man. Understanding immune functions and the requirements of the immune system to ensure efficient protection against infection and disease provide the core for developing vaccines and vaccination programs. Modern technologies now offer synthetic means for manipulating compartments of the immune system to advance development of more efficient vaccines. For these reasons, it is important for both veterinary and medical students to understand the functioning of the immune system in health and disease.

2. Veterinary immunology represents an own discipline

Considering the above facts, it is crucial to look at the immune system as the product of a long coevolution between different hosts and the microorganisms in their environment, benign as well as pathogenic (disease-producing). The constant host-microorganisms interactions throughout the evolution from primitive, multicellular organism to complex vertebrates have generated the complexity of the immune system as it is now known. Importantly, while the immune system of man and veterinary species follows the same principles, there are also important species-specific differences which can make the extrapolation of results from an animal model which is classically the mouse to other species misleading. This is of particular relevance for the study of host pathogen interactions, as both organisms are the product of a long co-evolution. This explains why the outcome of most infections is highly species-depend-

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ent and underlines the need to study the immunology of infectious diseases in their natural hosts, whenever possible.

As a matter of fact, this has driven the field of veterinary immunology with laboratories focusing on particular species such as cattle, sheep, goats, horse, pigs, dogs, cats, chicken or fish. Similar to human or murine immunology, it is necessary to establish reagents and methods for each of these species as they are not interchangeable. This requires an uncompromising commitment and an indispensable investment of time and financial resources, for which there is no alternative, if advancements want to be achieved. The progresses in veterinary immunology have been rewarding, not just for the veterinary field but above all by fostering the advancement of comparative immunology. This research permitted the identification of conserved elements of the immune system, which are of fundamental importance for its functioning.

3. Veterinary immunology at the Institute of Virology and Immunology (IVI) and the Vetsuisse-Faculty

The Institute of Virology and Immunology (IVI) at Bern is dedicated to teaching and research in veterinary immunology. The IVI is a product of a merger in Januray 2014 between the Institute of Veterinary Virology of the Vetsuisse-Faculty Bern and the former Institute of Virology and Immunology, a research facility of the Federal Administration. The present IVI still represents a Federal Research Institute but is now integrated into the Campus of the Vetsuisse-Faculty with both, the divisions of Immunology and Virology headed by university professors.

The teaching activities of the IVI are designed for veterinary students to help them understand the functioning and the role of the immune system in various diseases, such as infections, inflammatory diseases, autoimmune diseases and hypersensitivity reactions. Considering the diversity of veterinary species and their immune system, the focus is set on the most common species a Veterinarian will encounter.

Research activities of the IVI are located on two sites, the IVI campus in Mittelhäusern and the Vetsuisse campus. In both sites, a focus of our research is on mononuclear phagocytes and their interaction with microorganisms. Mononuclear phagocytes represent a class of leukocytes which are involved in innate immune responses. While the innate immune defenses are the most rapid in action, they lack specificity (for the pathogen) and robustness in terms of their longevity. Induction of adaptive immune

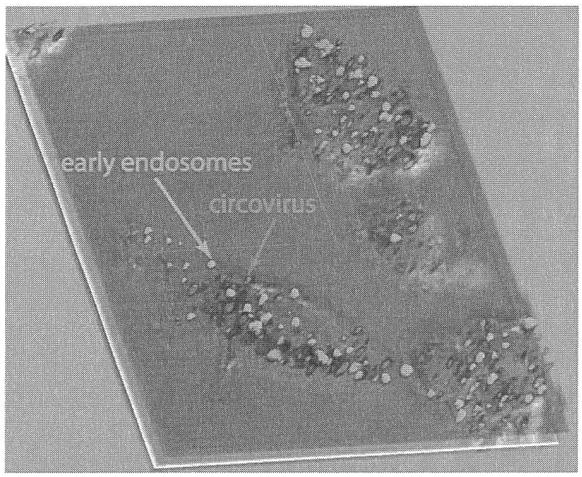

Figure 1 *(coulours see web version). «Under the Radar». Porcine circoviruses (red) persisting in antigen-presenting cells (grey) of the innate immune system. The virus is found structures (red) distinctive to those involved in degrading material internalized by the cell (green).*

responses provides this increase in specificity and duration of immunity against a particular pathogen. The mononuclear phagocytes are involved in the innate defenses, most prominently with phagocytic uptake and destruction of microorganisms, and inflammatory responses enhancing the activities of immune defenses. In addition, they are critical players for the antigen presentation processes essential for inducing the more specific and durable adaptive immune responses. They are thus at the center of the immune response. In the immunology laboratory in Mittelhäusern we focus on the porcine immune system which includes characterization of leukocyte populations. Thereby, we open the door to understanding better how virus pathogens interact with the cells of the innate immune system. An example of this work can be seen in Fig. 1, which shows porcine circovirus (in red) infecting antigen-presenting cells (grey) to persist in these cells by avoiding the cellular degradative processes (in green).

The laboratories in Mittelhäusern operate at the Biosafety level 3 and BSL-3-Ag, the latter offering maximum protection to personnel and environment, therefore permitting to develop research programs on the most dangerous livestock pathogens and a variety of zoonotic agents. Accordingly, we focus our work on studying the interaction of the porcine immune system with viral pathogens requiring such safety levels. At the laboratories in Bern, we focus mainly on ruminant mononuclear phagocytes and viruses targeting these cells.

In addition, to the immunology groups belonging to the IVI, the Vetsuisse-Faculty Bern hosts the laboratory of Professor Eliane Marti focused on clinical immunology and in particular on studying equine

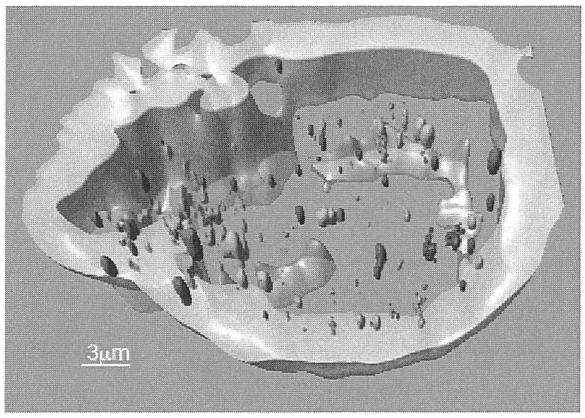

Figure 2 *(coulours see web version). Into the «Grand Canyon» of the antigen-presenting cells (light brown). Vaccine (green) is initially internalized into structures distinctive to those internalizing both are still far from the sites of antigen processing (blue) for presentation to the immune system.*

insect-bite mediated hypersensitivity reactions and equine mononuclear cells.

4. The pig as alternative model for human disease

The porcine immune system is relatively well characterized and found to share more similarities to the human immune system as compared to mice. Furthermore, many commercially available reagents are available for this species. This, together with physiological similarities in many organs system such as the respiratory and digestive tracts and the skin as made the pig an attractive alternative model for certain human disease in which the murine model has failed. Furthermore, the generation of transgenic pigs is nowadays easy, although relatively costly. Generally speaking, such models are required to bridge the gap in translating basic knowledge obtained in murine models to new therapies. The past has demonstrated that for certain diseases this translational gap cannot be bridged if only murine models are used. The laboratories of Professor Artur Summerfield and Dr. Kenneth McCullough are thus actively promoting immunological research for the benefit of both the animal and human. Through several projects funded by the Swiss National Science Foundation and the European Union, this knowledge on the porcine immune system has been elaborated to studies on zoonotic pathogens, developing vaccines for either porcine or human application. This requires comparative studies on the porcine and human immune system, and studies at the sub-cellular level to understand how antigen –presenting cells function when handling vaccines (Figs. 2 and 3). Importantly, our studies have led to the creation of new generation synthetic vaccines (see below). The latter areas of our research form the core themes in the laboratory of Dr. Kenneth McCullough, who is the current coordinator of Swiss National Science Foundation and European Union funded projects developing biodegradable vaccines against influenza virus.

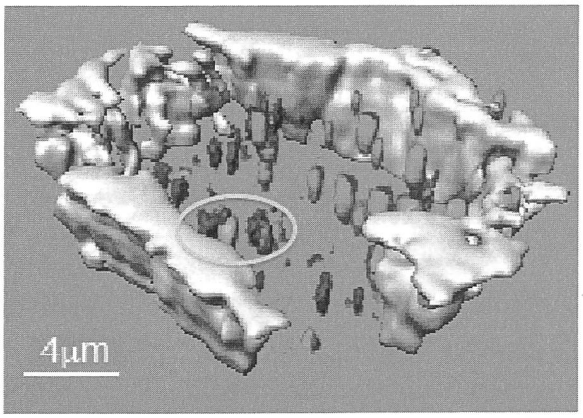

Figure 3 *(coulours see web version). The «Colosseum» of antigen-processing. As time progresses, both the vaccine (green) and dextran (red) come together (circled), as they are trafficked by the cell towards the antigen- dextran (red); processing compartment.*

5. Biodegradable, self-amplifying RNA vaccines: from pigs to humans

This research has been a major focus of the group led by Dr. Kenneth McCullough since 2006, identifying the appropriate pathways for efficient vaccine delivery (see Figs. 2–4).

The biodegradable, nanoparticle delivery vehicles involved primarily lipid-based and carbohydrate-based systems, hence their «attractiveness» to cells of the innate immune system, and their biodegradability. Thereby, an RNA molecule encoding the antigen is employed rather than the antigen itself, which allowed for a highly pure vaccine and multiple copies of the antigen produced by translation of the RNA. Through the nanoparticle delivery vehicle, the vaccine could be targeted to the antigen-presenting cells, wherein the quantities of antigen produced far exceeded that provided by a more conventional protein-based vaccine. The use of immune cells from pig donors provided the means for studying delivery to and interaction with the immune system to a degree impossible when employing cells from human donors. While vaccines based on classical mRNA molecules have a clear efficacy, they are restricted by their non-replicative nature. Elaboration of the RNA vaccine approach has employed larger, self-amplifying (self-replicating) RNA molecules derived from replicon technology. This comes from a close collaboration since 2007 between the groups of Dr. Kenneth McCullough and Dr. Nicolas Ruggli of the Virology Department at the IVI. The replicon RNA not only encodes for the vaccine antigen(s) of choice, but also the endogenous proteins necessary for the replication and therefore amplification of the RNA within

the cells; such replicons are also referred to as self-amplifying mRNA. The validity of this approach using biodegradable, nanoparticle delivery of self-amplifying replicon RNA vaccines has now been proven in both cell-based systems and in vaccinated animals.

6. Goats, sheep and their lentiviruses

The focus of our research in this field, led by PD Dr. Giuseppe Bertoni, is to understand the interactions between the small ruminant lentiviruses (SRLV) and the immune system of their host species, i.e. goats and sheep. These viruses, which are closely related to the human immunodeficiency virus (HIV), share with their human counterpart a marked tropism for the mononuclear phagocytes without, however, infecting T cells. This permits us to study the pathogenesis of lentiviruses in the context of an intact immune system. SRLV have been the target of a long and successful eradication campaign in Switzerland, which drastically reduced the number of infected goats from around 80% in the eighties, to less than 1% and permitted the complete elimination of clinical disease manifestations, such as arthritis, in these species. This notwithstanding, low virulence stains of SRLV are still circulating in goats and sheep. Recently, we have focused our research on understanding the molecular determinants of attenuation in these strains, which represents a perfect example of a successful coevolution between viruses and their hosts, or, more precisely, their immune system. In this context, we aim at understanding the virus and host immune system factors determining the fragile balance between disease and pacific cohabitation. ■

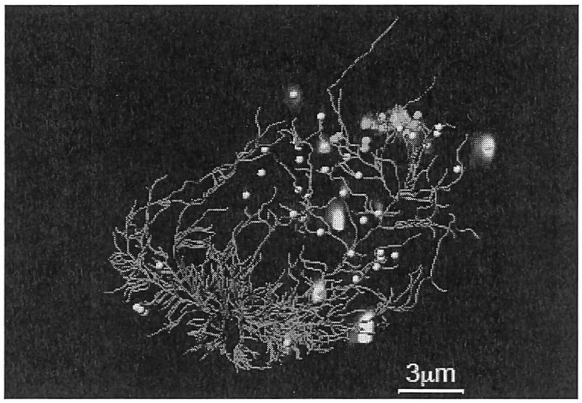

Figure 4 *(coulours see web version). The «Tentacles of Doom». Microtubules (red) in the antigen-presenting cells form the «tram-lines» of the cell, along which vesicles carrying the vaccine (green) are transported to the degradative compartments, including those involved in the antigen-processing (blue) required for antigen-presentation.*

Modelle zur Untersuchung der Krebstherapieresistenz

Sven Rottenberg*

Eine der grössten klinischen Herausforderungen in der Human- und Veterinärmedizin ist die Bekämpfung der Therapieresistenz. Der Beitrag der Veterinärmedizin zum Verstehen und zur Vermeidung von Antibiotikaresistenzen ist unter Punkt G beschrieben. Daneben ist für den Menschen insbesondere die Resistenz gegen eine Krebstherapie ein zentrales klinisches Problem. Eine lokale Therapie (z.B. chirurgische Entfernung und Radiotherapie) von Tumoren ist häufig sehr wirkungsvoll. Für Patienten mit ausgesäten Tumoren muss allerdings eine systemische Therapie (z.B. Chemotherapie) angewendet werden. Hier sind die Chancen einer kompletten Heilung für die meisten epithelialen Neoplasien leider gering, auch wenn es neue Durchbrüche wie z.B. in der Immuntherapie gibt. Die meisten Patienten mit klinisch erkennbaren Metastasen entwickeln früher oder später eine Resistenz gegen alle verfügbaren Mittel, und für diese Menschen ist die Krebstherapieresistenz die häufigste Todesursache. Die genauen Ursachen dieser «Panresistenz» sind allerdings oft unklar, selbst für Medikamente welche bereits seit Jahrzehnten zum Einsatz kommen. Um die Therapieresistenz zu erklären sind eine Vielzahl von Mechanismen untersucht worden. Diese beinhalten das fehlende Erreichen der Zielmoleküle in den Krebszellen, Veränderungen der betroffenen Moleküle, vermehrte DNA Reparatur, Blockierung der Apoptose, spezielle Abwehreigenschaften von Krebsstammzellen, epitheliale zu mesenchymaler Transition, Chromatinveränderungen, Veränderungen der Signaltransduktionswege und die Expression von Faktoren des Tumor-assoziierten Stromas, welche das Überleben der Krebszellen begünstigen. Einige dieser Mechanismen sind auch in Patienten validiert worden. Ein klassisches Beispiel sind die Mutationen der ATP-Bindungstasche im Zusammenhang mit der Resistenz gegen Tyrosinkinaseinhibitoren. Für viele der beschriebenen Mechanismen ist allerdings unklar, ob sie wirklich für Patienten relevant sind, denn die gewonnene Information stammt von isolierten Zelllinien. Inwieweit die Resultate von 2D Zellkulturen auf die Antwort des ursprünglichen Tumors extrapoliert werden können, ist allerdings sehr fraglich. Es ist dann auch nicht unerwartet, dass viele der anschliessenden

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