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Environment–KHV–carp–human linkage as a model for environmental diseases

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Abstract To predict outbreaks of infectious disease and to prevent epidemics, it is essential not only to conduct pathological studies but also to understand the interactions between the environment, pathogen, host and humans that cause and spread infectious diseases. Outbreaks of mass mortality in carp caused by *Cyprinid herpesvirus 3* (CyHV-3), formerly known as koi herpesvirus (KHV), disease have occurred worldwide since the late 1990s. We proposed an environment–KHV–carp–human linkage as a conceptual model for “environmental diseases” and specify research subjects that might be necessary to construct and shape this linkage.

Keywords Environmental disease · Koi herpesvirus · *Cyprinid herpesvirus 3* · Common carp · *Cyprinus carpio carpio* · Environment–pathogen–host–human linkage

Introduction

The outbreak and rapid spread of emerging infectious diseases, such as new influenza, bird influenza and foot-and-mouth disease (*Aphthae epizooticae*), are serious global environmental problems that threaten humans, livestock and wildlife worldwide (Daszak et al. 2000; Jones et al. 2008).

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In general, preventive measures against infectious disease have been developed by focusing primarily on rapid and accurate diagnostic methods as well as preventing the spread of disease after an outbreak. Although pathological understanding has developed, the behavior of pathogens in natural environments and the linkages between pathogens and humans that induce and spread infectious disease are still unclear (Kawabata 2011).

Based on the hypothesis that anthropogenic environmental changes mediate the outbreak and spread of disease (Kiesecker et al. 2001; Johnson et al. 2010), to respond to emerging infectious diseases proactively before they become major health problems, it is essential not only to conduct pathological studies but also to clarify the interactions between environments and humans that generate infectious disease.

Disease caused by *Cyprinid herpesvirus 3* [CyHV-3, formerly known as koi herpesvirus (KHV)] is a global environmental problem. Since the late 1990s, KHV has caused outbreaks of mass mortality in carp (Pokorova et al. 2005; Matsui et al. 2008), which have long been part of the human food chain and culture (see e.g., Akimichi 2005; Nakajima et al. 2010).

The objectives of this note were to introduce a concept of an environment–KHV–common carp–human linkage (KHV disease linkage, Fig. 1) as a conceptual model for environment–pathogen–host–human linkages, as shown in the middle column of Fig. 2, by synthesizing various levels of subjects, leading to a new field of study—“environmental disease” science—that clarifies how human actions cascade through specific environments, potentially advantaging disease-causing pathogens, and to describe the direct and indirect links between environmental change and pathogen–host–human interactions. We also propose specific fundamental research subjects that will be necessary to construct the KHV disease linkage model.

KHV disease linkage

We will focus on the relationships between the human-modified littoral area of Lake Biwa, Japan, KHV (Ilouze et al. 2006), common carp (*cyprinus carpio carpio*) (hereafter carp) (Stuart and Jones 2002), KHV disease, and humans (KHV disease linkage) as a conceptual model for “environmental diseases” that appear and spread in human-modified environments (Fig. 2). This KHV disease linkage system has three advantages for study: (1) under natural conditions, KHV infects only carp, meaning that the only factor affecting increase in KHV abundance is carp; (2) we can conduct field surveys and experiments to verify the interaction under various conditions to clarify the environment–KHV–carp–human linkage; (3) it involves parameters common to other diseases, such as temperature, densities of pathogen and host, stress subject to disease, which will allow us to establish a conceptual model for the emergence and spread of diseases (Kawabata 2011).

Research direction

Through proceeding to construct a KHV disease linkage, research will be aimed at obtaining the following outcomes. At our intensive study site, Lake Biwa, we will (1) clarify how modified littoral areas affect the ecology of both KHV and carp, (2) map the distribution of KHV, (3) map the distribution of carp, (4) map stressors of carp, (5) visualize the potential occurrence of KHV disease and diagnose the occurrence of KHV by using landscape observation, (6) evaluate the effects of carp disappearance on ecosystem and economy, and (7) predict the emergence of KHV disease by combining the results from (1) to (4) above.

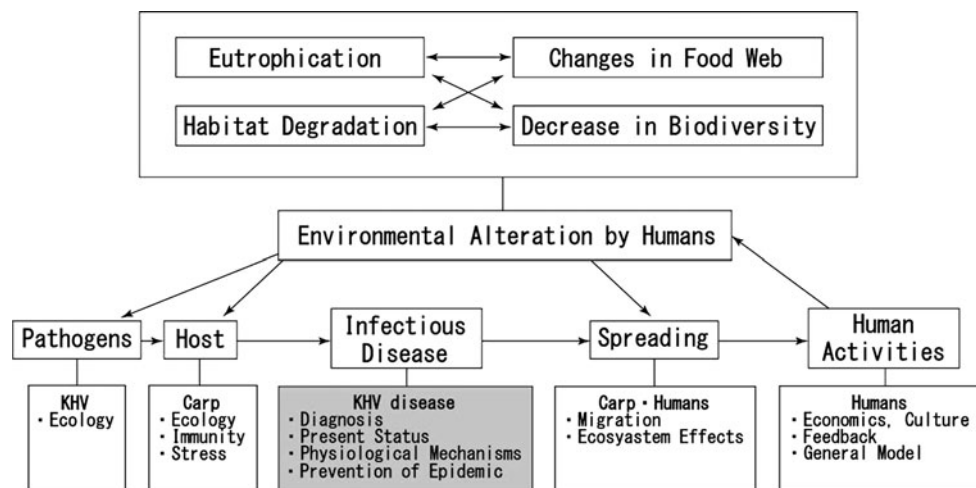


Fig. 1 Environment–KHV–carp–human linkage. Research fields still remain with many unrevealed subjects, except the field of KHV disease indicated with a shaded box (modified from The RIHN

prospectus, 2010–2011, p 14, http://www.chikyu.ac.jp/archive/brochure/2010/index_e.html)

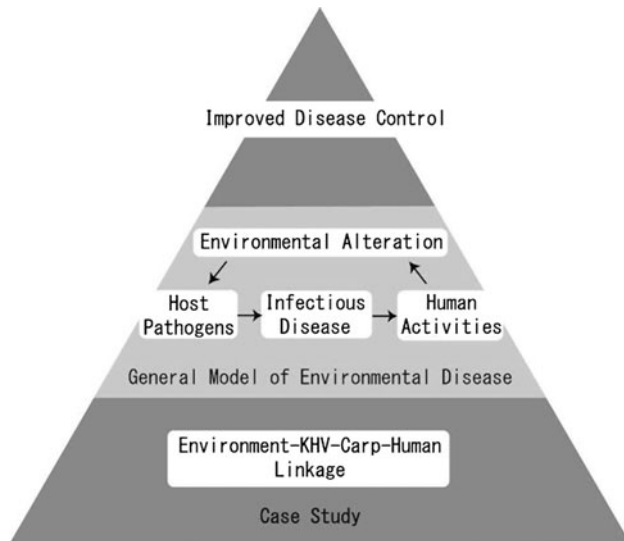


Fig. 2 Development of environment–KHV–carp–human linkage model to establishment of “environmental disease” science for improved disease control as ultimate goal through the application of the conceptual model of the environment–KHV–carp–human linkage to other infectious diseases (modified from The RIHN prospectus, 2010–2011, p 15, http://www.chikyu.ac.jp/archive/brochure/2010/index_e.html)

After constructing the KHV disease linkage, we will (8) extrapolate it to other infectious diseases (O’Brien et al. 2000; Bruggemann et al. 2006) to explain how environmental alterations induce these diseases, to find common structures among these diseases, and to establish a general concept for the emergence and spread of disease (general model for environmental disease in Fig. 2). Finally (9), we suggest ways to prevent or minimize the emergence and spread of infectious diseases for improved disease control that will ensure the safe coexistence of hosts with pathogens (Fig. 2), and we will (10) contribute to the development of the field of “environmental disease” sciences.

This research is embodied by a verification study aimed at developing methods of preventing the rapid and large-scale spread of infectious disease from “environmental disease” science. Our research in this area is innovative, and we expect to achieve results that will contribute to creating an academic discipline devoted to solving the global environmental problem of infectious disease. To ensure effective results, this research integrates various disciplines from molecular biology to environmental sciences and the humanities.

Through an understanding of the KHV disease linkage, we will also propose environments that prevent the outbreak and spread of KHV. This will provide us with knowledge on how to conserve carp—an important source of food for inland people around the globe (Food and Agriculture Organization of the United Nations, Fishery Statistical Collections/Global Production; <http://www.fao.org/fishery/statistics/global-productions>) and an indispensable component of aquatic ecosystems.

Little available data on the linkage

Although it may appear that sufficient data on KHV and carp ecology, as well as human relations with carp (Akimichi 2005), are available to describe KHV disease linkage, the findings of a recent review revealed that little useful data for constructing this linkage exists. No studies relevant to verifying this linkage exist, because (1) these issues were of lesser importance and urgency than research in existing fields; (2) current methodology is insufficient to address these issues; (3) it is difficult to verify the linkages between environmental change, pathogens, and humans; and (4) few researchers and institutes have promoted synthetic and comprehensive research on linkages that involve various system levels, ranging from molecular biology to environmental sciences including human society (Kawabata 2011).

Regarding methodology, researchers have not established a method for detecting and quantifying KHV in aquatic environments (Matsui et al. 2008). This has been an obstacle to understanding KHV dynamics such as where, when, or how much KHV exists in natural environments. Regarding the ecology of carp, experts do not know where, when, or for how long carp move in human-mediated environments. This information is essential to determining where KHV disease may occur in a natural environment. Stress might be a trigger for developing disease (Barton 2002); however, it is unclear how carp are stressed under some human-mediated environmental conditions. No data are available on how carp immunized against KHV behave as carriers of KHV in natural environments. This is a very important subject for understanding how KHV disease spreads. Only few data are available on the role of carp in a lake ecosystem (Matsuzaki et al. 2007).

These data are necessary to describe the KHV disease linkage that is useful to predict the emergence and spread of KHV disease, to make recommendations to alleviate KHV disease, and to build a conceptual model of “environmental disease” that will apply to other diseases.

From intensive study site to global areas

When a problem is observed on a global scale, research should focus on areas where the problem typically occurs. The data obtained should then be extrapolated to other areas on a global scale. Comparable and experimentally controllable areas are necessary to conduct studies with predictability. Our project includes these aspects of study areas. To construct the KHV disease linkage, field surveys are being conducted primarily at Lake Biwa, Japan, and we are also accumulating and synthesizing both new and existing data from Lake Biwa, Japan, where researchers from various disciplines and fishermen have accumulated much data. The KHV disease linkage will be applied to Lake Erhai, China to

provide suggestions of how to manage the lake to lessen the probability of an outbreak of KHV disease. China is responsible for almost the entire global production of carp (Food and Agriculture Organization of the United Nations, Fishery Statistical Collections/Global Production; <http://www.fao.org/fishery/statistics/global-productions>). Lake Erhai is an inland lake in China where an outbreak of KHV has not yet been reported.

The practical application of this model to such an important region is critical to attenuating the global problem of KHV disease. The KHV disease linkage derived from Lake Biwa will be modified to apply to other infectious diseases in other places, to suggest environments that might prevent the outbreak and spread of infectious disease, and to demonstrate how to facilitate the safe coexistence of humans with pathogens.

Data obtained on the linkage

We have established a method for detecting and quantifying KHV in natural waters (Minamoto et al. 2009a; Honjo et al. 2010). When we proposed our KHV disease linkage project, we did not know where and when KHV existed other than in infected carp. Using our detection and quantification method, we revealed that KHV remains in both lakes and rivers long after the outbreak period (Minamoto et al. 2009a, b). Spatial and temporal changes in water temperature in the human-degraded littoral zone are more homogenous than those in natural areas (Yamanaka et al. 2010). This has the potential to affect carp behavior, immunity to KHV, and stress (Takahara et al. 2011). A mathematical model was used to show that temporal local high densities of carp with decreasing breeding habitats due to human activities exemplified outbreaks of KHV disease (Yamamura et al. 2011). We also discovered that only carp larger than 30 cm in length had serum anti-CyHV-3 antibodies (Uchii et al. 2009). This indicates that carp behavior due to size is a key factor in determining the site and spread of an outbreak. We also found that breeding habitats can become hotspots for transmission of KHV disease if carp aggregate for mating and activation of KHV occurs during the breeding season (Uchii et al. 2011). We established a method for quantifying stressors in the water modified from that of Ellis et al. (2004) without causing stress to living carp. This will enable us to conduct experiments to discover the relationship between water temperature and stress in carp (Takahara et al. 2011).

Discussion

Although we have described the features of several components of the KHV disease linkage, further study of several more key areas will be required to describe the KHV disease linkage as a whole, which is formed by links of cause and effect. These are as follows:

Human activities

Although we are focusing on Lake Biwa, which has experienced intensive environmental alterations due to construction of a road along the lake shore resulting in the destruction of shallow habitats in the lake, to ensure the applicability of the KHV disease linkage to other cases we also need to focus on Lake Erhai, China, where the same situation as in Lake Biwa will occur within a few years. Four environmental alterations mediated by humans were considered in this paper: habitat degradation, eutrophication, changes in the food web and decrease in biodiversity (Fig 1). These factors interact with each other; therefore, the relationships among these four factors should be the subject of further studies. We also have to deal with economic and cultural losses caused by KHV disease that might affect subsequent environmental conservation policies that lead human actions. KHV disease is another aspect to be considered by people in the context of lake system conservation because it is assumed that such diseases are related closely to environment degradation due to human activities.

KHV

We have developed a method for detecting and quantifying KHV in natural waters. A modification of this method can be applied to detect KHV in sediment, plankton (Minamoto et al. 2011), benthic organisms and carp excrement. We regard this subject as essential to understanding the environment–KHV–carp–human linkage. It is likely that the DNA of KHV is stable, but that virus infectivity is unstable. We should consider this point to explain the spread of KHV disease. We need to develop an innovative technique to detect infective KHV rapidly on site in aquatic ecosystems. This will enable us to create a diagnostic map of global KHV disease that will help researchers understand how KHV spreads and establish policies to prevent the spread of KHV disease. This technique will likely be applicable to other infectious diseases. We should study carriers and their ecology. We regard carriers of KHV other than infected carp as important factors in the spread of KHV. KHV disease was first found in a farm of *Cyprinus carpio koi* (ornamental carp) in England in 1996, followed by spread of KHV disease worldwide among common carp in both aquaculture and wild-populations. This suggests that KHV evolved in aquaculture and one of the candidates implicated in transmission is humans transmitting KHV indirectly to other areas by transporting infected carp. The transportation system of carp by humans should thus be clarified.

Carp ecology

We have insufficient data on carp behavior. Measuring stable isotopes of carp samples from various sites both

with and without the KHV antibody is one of the methods required to clarify roughly the locations carp mainly inhabit. Telemetry is another candidate method to clarify precisely the spatiotemporal behavior of carp.

KHV disease

Latent infection is considered as one mechanism responsible for the spread of KHV (Eide et al. 2011). We found carp with KHV in both its brain tissue and gills outside of the breeding season (Uchii et al. 2011). Therefore, it is necessary to clarify the conditions required for reactivation of latent KHV to understand KHV persistence over long periods of time. Water temperature fluctuations could be a potential stressor for carp (Takahara et al. 2011), because carp metabolism is regulated by water temperature. We regard stress as one of the conditions needed for reactivation. Thus, experiments on carp infected with KHV under the stress of changes in water temperature are required in order to understand the relationship between stress and reactivation of KHV.

An encounter between KHV and carp is the first event leading to the outbreak of KHV disease. Visualization of the place and time of a possible outbreak is one of our scheduled outputs. According to our finding that KHV exists throughout the lake (Minamoto et al. 2009b), research on such visualization should focus on KHV behavior both with and without carp. We also need to clarify the environmental characteristics of places where both KHV and carp are present.

Significance of carp

A fisherman is involved in our project as a co-researcher. Information from sources other than scientists and the accumulated experience of fishermen should be used to advantage. The history of fishery should be studied in order to understand human activities on the lake. We will study how humans have depended on fisheries in the past to understand how the present culture of eating carp in Japan is diminishing. It is also important to clarify the value of carp as a food, and as a cultural item, as well as its ecological role, and then evaluate the economic, cultural and ecological impacts of the disappearance of carp.

Environment–KHV–carp–human linkage

We should discuss how we will be able to integrate the results discussed above into the KHV disease linkage. Such integration will allow measures to prevent the occurrence and spread of infectious disease to be proposed if we can identify where these outbreaks are likely to occur. Our KHV disease linkage will be applicable to the other fish that require similar habitat conditions. Water temperature and stress are essential environmental factors that regulate fish metabolism, affecting their ecology and

susceptibility to various infectious diseases. However, we need to investigate the specific degree of these factors needed to cause disease. Such measures will also reduce the economic losses caused by such outbreaks.

Conceptual models of disease

Although it is very difficult to apply the conceptual model of the environment–KHV–carp–human linkage to other infectious diseases, we will be able to compare various infectious diseases from the viewpoint of this linkage to find essential, common and specific elements, such as mortality rates and stress, for defined diseases in order to be able to describe the emergence and spread of disease. We refer to Legionnaires' disease in Asia (Yamaguchi et al. 2011) as an example of an application of the conceptual model of the environment–KHV–carp–human linkage. The authors pointed out that a habitat favorable for the intermediate host amoeba was created by changes in human water usage, and a critical point of the linkage that could be targeted to alleviate the outbreak was then suggested. The key scientific subject is to find potential factors that promote viral evolution toward high virulence, because viral virulence might affect strongly the dynamics of the linkage. Environmental factors involved in gene transfer (Matsui et al. 2003; Ueki et al. 2004), predation of pathogens by microbes (Friman et al. 2009), and development of the host immune system (Penman and Gupta 2008) must be considered as candidate driving factors for the evolution of virulence.

Improved disease control

Elimination of infectious disease is not the purpose of our study. It is generally impossible to eliminate pathogens (Ewald et al. 1998). Researchers should understand the role of pathogens in sustaining and evolving in the context of the human ecosystem. We would like to find a way that humans and pathogens can safely coexist to ensure our "futurability" (The RIHN prospectus, 2010–2011, http://www.chikyu.ac.jp/archive/brochure/2010/index_e.html)

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