QnAs with Harald zur Hausen

The first carcinogenic virus was discovered in chickens in 1911.

More than 70 years later, Harald zur Hausen demonstrated that human papillomavirus (HPV) can cause cervical cancer, for which he garnered the 2008 Nobel Prize in Medicine or Physiology. A professor emeritus at the German Cancer Research Center and recently elected member of the National Academy of Sciences, zur Hausen's contributions to the field of virology have reshaped our understanding of the connections between infectious and chronic diseases. PNAS recently spoke with the Nobel laureate about HPV, undercooked beef, and scientific "dogma."

PNAS: In general, how do viruses cause cancer?

zur Hausen: There are very different modes of interaction of viruses with the host cell. Roughly we can differentiate between viruses that operate directly by inserting oncogenes into the host cells and those that act as what we call "indirect" carcinogens. Indirect carcinogens might cause immunosuppression and thus activate other oncogenic viruses, or they might cause chronic inflammatory reactions leading to mutagenic oxygen or nitrogen radicals. Importantly, we do not know of a single virus—not even another infectious agent linked to cancer—which causes cancer as a direct consequence of infection. In each individual case, a number of modifications in the host cell genes have to be acquired before the development of cancer. These changes usually impair signaling cascades which would otherwise protect us from the cell's conversion to a malignant tumor.

PNAS: Is the carcinogenic mechanism of HPV direct or indirect?

zur Hausen: Direct. The progression from infection to cervical cancer requires something like 15–25 years. Within this period, a couple of modifications occur within the host cell DNA. These mutations are due in part to a low degree of expression of viral oncoproteins and are in part due to other chemical and even physical factors.

PNAS: Oncogenic viruses harm their hosts by causing uncontrolled cellular proliferation. However, traditional viruses cause harm during their lytic phase by replicating extensively and bursting the host's cells. Are these two paradigms in conflict?

zur Hausen: No, because replication incompetence seems to be a precondition for

Harald zur Hausen.

cancer development. For example, virtually all of us are infected by human polyomaviruses, which are usually nontumorigenic. However, if you transmit them to other species where they cannot replicate, they can turn into oncogenic agents.

PNAS: You are building a case for the link between colorectal cancer and the transmission of bovine viruses through the consumption of undercooked beef. What sparked your interest in this area?

zur Hausen: I began to consider that some of our domestic animals may harbor viruses that are nonpathogenic for the animals but upon transmission to a replication-incompetent host—in this case humans—could become carcinogenic. Looking at the geographical epidemiology of colorectal cancer, it struck me that colorectal cancer is basically restricted to populations that feed to a large extent on beef.

PNAS: What is the current explanation for this correlation?

zur Hausen: Red meat consumption as a risk factor for colorectal cancer has been established in many cohort studies. Since 1977 it has been suggested that the causative agents were chemical carcinogens produced during the cooking of the meat. This sounds reasonable, but recently a couple of publications demonstrated that the same cooking processes, before poultry or fish consumption, produce similar quantities of these chemical carcinogens but do

not increase the risk for colorectal cancer. So then we started to look for agents that might be relatively thermal resistant, particularly in beef when it is prepared medium-cooked or rare. In these beef dishes, the temperatures are about 40–70 °C in the center part, where the meat is still relatively rare, and those are temperatures at which some viruses, the theoretically suspected agents, survive very happily without any significant loss of activity.

PNAS: Some of your earliest work showed that Epstein–Barr virus could cause lymphoma, but your work on HPV is better recognized. Why?

zur Hausen: The fact that cervical cancer is the second most frequent cancer in women globally probably made it more interesting for the public. When we initially demonstrated that Burkitt's lymphoma cells contained the viral DNA in a latent form, that was, for me, a first clear-cut demonstration that in humans the situation exists which is quite analogous to lysogenic bacteria containing phage lambda genomes. It was, for me, the proof of the concept that I had been following since my student times.

PNAS: How did you deal with the initial skepticism surrounding your HPV discovery?

zur Hausen: It took quite some time before we could identify and isolate true cervical cancer viruses. During this period, between 1972 and 1983, there was a lot of criticism when I talked about it, but I originate from a part of Germany where the people are known to be relatively stubborn, so maybe that is the reason that it didn't affect me much.

PNAS: How do you explain the evolution of scientific knowledge to the public so that they can understand challenges to scientific "dogma"?

zur Hausen: Science is a fluctuating process, in my opinion, and we need to explain that data we have obtained in the past may be indeed overturned by newer developments, and this is in the nature of science itself. It needs to happen like that; fortunately it does happen from time to time. So we will always experience, in certain intervals, specific dogmas being overturned. Science needs a continued fluctuation; it needs to reinterpret data in the view and in the light of what has been recently seen and obtained; and I think this is something that needs to be freely and openly discussed with the public.

Catherine Kolf, *Mirzayan Fellow*