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Q&A Harald zur Hausen

On the case

A Nobel prizewinner for pinning cervical cancer on human papillomavirus, Harald zur Hausen still investigates viruses. Nature Outlook *talks to the medical doctor–turned–virologist about other possible culprits.*

What first raised your interest in HPV?

I was only interested in cervical cancer. I picked up on papillomaviruses by looking into the literature from the 1930s: researchers such as Richard Shope and Peyton Rous had investigated lentil-like structures on wild US cottontail rabbits. They found that taking extracts from these lesions and infecting domestic rabbits produced similar warts that converted gradually to malignant tumours. I also found a few anecdotal reports that genital warts in humans occasionally converted into malignant tumours. These findings triggered the idea that there may be an agent in the genital lesions that could also cause cervical cancer; perhaps this agent has a different cancer-causing potential in the cervical mucosa than in the external genital skin.

Since I had seen papillomavirus particles in genital warts, I thought HPV would be a good candidate. However, as there are few particles in genital warts, it took us a long time to characterize and isolate HPV type 6 and it was very disappointing not to find HPV-6 in cervical cancer samples. We kept looking, however, and a year later we found a related virus in genital warts: HPV-11. Using HPV-11 as a probe, we finally managed to isolate the distantly related HPV-16 and HPV-18 and link them to cancer. It was not a Eureka moment.

What are the prospects for cancer prevention?

There is a good chance of drastically reducing cervical cancer by vaccination. In Australia, where there is more than 70% coverage, the data are clear cut — the precursor lesions are being prevented. There's no evidence yet that cancer is being prevented, as this takes time. The average latency is 15–25 years; since the vaccine is 6 years old, we still have a 10–20-year wait. But look at hepatitis B. In Taiwan where there is compulsory vaccination since 1984, the rate of liver cancer has dropped by 70%. Something similar will happen with cervical cancer.

Can we eliminate HPV?

HPV-16 and -18 could probably be eliminated if we have a global programme. You could theoretically achieve this by vaccinating only girls, but you would need very high coverage. I'm a strong advocate for vaccinating boys as well: we'll reach the goal much faster by vaccinating both sexes. The disadvantage is that the cost is very high.

How common is HPV?

HPV is part of an enormously heterogeneous family of viruses with more than 200 individual genotypes. Virtually every part of our skin is infected by papillomaviruses, and some prevent apoptosis (cell death), cutaneous types in particular. If skin cells survive after mild damage by ultraviolet radiation, this might provide some protection. I suggested recently that we examine white and black skin to see whether there are differences in the viral load and to determine whether there is an evolutionary advantage in having large amounts of cutaneous HPVs. But there is another side to blocking apoptosis: if the cell sustains too much damage but doesn't die, it could turn cancerous.

There is an old suspicion that HPV is involved in non-melanoma skin cancer. For many cancers, if the number of cases increases in line with imunosuppression, an infectious agent might be involved. In breast cancer, for example, immune suppression might have a protective effect that we don't yet understand. In the majority of skin cancers, there is fewer than one copy of HPV DNA per cell, which suggests the virus is not a major player.

Could microbes lie at the root of more cancers?

Based on epidemiological characteristics, it is very likely, particularly in some leukaemias and lymphomas. At the moment, less than 10% of the total leukaemia/lymphoma burden is attributable to viruses or bacteria.

Colon cancer is interesting. If you look at its geographic incidence, it is linked to areas with high red-meat consumption. For example, in most regions in India, where beef is not consumed, it is a rare form of cancer. The only exception is Mongolia where they have low rates of colon cancer and eat a lot of red meat, but there they eat yak. It's not too far fetched to think there might be a cow-specific infectious agent.

We are trying to identify agents in cattle and in humans. There is evidence that some exist, but we don't know whether they are carcinogenic or not. These are anelloviruses, specifically torque teno viruses (TTVs). They have some interesting properties: micro-TTVs, for instance, are totally rearranged tiny molecules that replicate autonomously — why and how, we don't understand. In addition, there are chimaeric forms, consisting of TTV DNA and host-cell sequences derived, in part, from growth-promoting genes — some of which are known to be important in the development of cancer. ■

Interview by **Michelle Grayson**, *senior editor for* Nature Outlook *in London.*