New pathogens in beef and cow's milk contributing to the risk of cancer

A team of researchers led by Nobel laureate Prof. Dr. med. Dr. h.c. mult. Harald zur Hausen has discovered a new type of infectious agent in dairy and meat products produced from European cattle that increases the risk for colon and breast cancer. These so-called Bovine Meat and Milk Factors (BMMFs) are small DNA molecules that are similar in sequence to both bacterial plasmids and certain viruses.

Prof. Dr. med. Dr. h.c. mult. Harald zur Hausen

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When Professor Harald zur Hausen was awarded the Nobel Prize in Physiology or Medicine for the discovery of carcinogenic human papillomaviruses in Stockholm on 7th December 2008, he concluded his Nobel Lecture with the following words: "The intention of this lecture is to raise interest in these topics and to stimulate interest and innovative studies in the potential role of infectious agents in some of the major human cancers. ... Research on infectious causes of human cancers has great potential for future surprises." The former DKFZ chairman did in fact come up with such a surprise recently: at a press conference at the German Cancer Research Center (DKFZ) in February 2019 zur Hausen presented - together with virologist Prof Dr. Ethel-Michele de Villiers and molecular biologist Dr. Timo Bund - research on new infectious agents found in beef and cow's milk that increase people's risk for developing colon and breast cancer.

Epidemiological information

At the press conference in February, Prof. zur Hausen discussed the many studies around the world which show a link between the consumption of red meat and dairy products and the incidences of colon and breast cancer. Regions such as North America, Argentina, Europe and Australia, where large quantities of beef and dairy products from European cattle are consumed, have a high risk for colon and breast cancer. However, a low incidence for both cancers has been recorded in Mongolia, Bolivia and India, countries that breed and consume mainly Asian zebus (in the case of Mongolia zebu half-breeds, but also yaks). At the same time, some Indian states that used to have extremely low breast cancer rates are now experiencing higher levels of breast cancer, potentially linked to the introduction and consumption of European dairy cow products. Data from Japan and Korea reveal a dramatic increase in the previously extremely low levels of colorectal cancer after enhanced meat products were made from European beef imports. The suggestion that milk and dairy products contribute to cancer risk is substantiated by the observation that people with lactose intolerance have much lower rates of breast cancer compared to their lactose-tolerant siblings or parents.

The analysis of epidemiological data suggests that European cattle carry pathogens that increase the risk of breast and colon cancer. Zur Hausen pointed out that although most viral pathogens are very host-specific, they can also infect cells of other species. A long-lasting infection can then lead to a malignant transformation of the cells. Thus, pathogens adapted to livestock can be transmitted to humans and occasionally cause cancer.

A new type of pathogen

Initially, Harald zur Hausen and Ethel-Michele de Villiers, the former head of the Department of Tumour Virus Characterisation at the DKFZ, were looking for viruses that they thought could be cancer risk factors. However, after having examined hundreds of blood sera of European dairy cows and numerous samples of commercially available milk and milk products from supermarkets, zur Hausen, de Villiers and their co-workers instead found single-stranded circular DNA molecules with sequences homologous to a plasmid of the bacterium Acinetobacter, a human pathogen that can cause a variety of infectious diseases, but is also known to infect cattle. As they were discovered in cattle meat and dairy products, the DNA molecules are referred to as "Bovine Meat and Milk Factors" (BMMFs). Since their initial discovery, over 120 different types of BMMFs have been isolated.

De Villiers reported that all BMMFs carry a gene that encodes the so-called "Rep" protein (replication initiator protein), which the viruses need to replicate. This makes them similar to CRESS (circular Rep-encoding single-strand DNA) viruses. To date, the nature of the pathogens has not been defined clearly; but it is assumed that they represent a new type of pathogen, with

properties that lie between those of viruses and bacteria.

Left: above, a yak (Bos mutus), below, a zebu or humped cattle (Bos indicus) - two cattle species that are not suspected of carrying BMMFs. Right: two breeds of European cattle (Bos taurus), in which BMMFs are found and whose meat and milk are associated with an increased risk of cancer.
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The researchers detected BMMF antibodies in the blood serum of both healthy and cancer patients, which was evidence that an exposure to BMMFs must have occurred. Timo Bund and his research group at the DKFZ were able to show that BMMFs can be replicated and transcribed in a human cell line, resulting in the expression of the Rep protein. The researchers also carried out a histological examination of the spread of the pathogens in the human body using highly sensitive Rep protein antibodies; amongst other tissues, they detected BMMFs in colon and breast tissue. While BMMF sequences were not found in colon cancer cells, BMMF proteins were discovered in the connective tissue layer below the intestinal mucosa, the lamina propria. Here, the team also detected macrophages and oxygen radicals, a finding that suggests that inflammatory processes were taking place. "We therefore assume that BMMFs trigger DNA mutations in the intestinal epithelial cells following a prolonged inflammatory reaction. And this can then lead to colon cancer," said Bund.

Protection against BMMF infections?

The findings are in line with zur Hausen's and de Villiers' hypothesis that BMMF infections most likely occur in early infancy in children that are being fed dairy products after they have been weaned and at a time when the child's immune system is not yet mature enough to fight off pathogens. The researchers hypothesize further that these children will develop an immunological tolerance to BMMFs that could later favour the development of certain cancers. According to the researchers' hypothesis, the pathogens themselves induce chronic inflammation, which can trigger the onset of cancer in colon and breast tissue. The researchers assume further that the onset of disease occurs decades after infection. This would mean that BMMFs have an indirect carcinogenic effect - comparable to, for example, chronic liver infection caused by hepatitis C viruses and the development of liver cancer.

Does this mean we need to refrain from consuming milk and beef in order to reduce our risk of developing cancer? As the blood of adults has been shown to contain BMMF antibodies, refraining from consuming milk and beef during adulthood would have little effect. Zur Hausen believes that this is because adults already carry the infection. The vaccination of babies, or the vaccination of cattle to prevent the transmission of BMMFs has the potential of being able to prevent disease, but this is still far from being implemented. It is currently being investigated whether the Rep protein can induce protective immunity.

It is known that infants can be protected against infection with a variety of pathogens (including HIV) with long-term breastfeeding. Effectors in this situation might be specific sugars in human milk that prevent the adherence of the pathogens to receptors on the pathogens' cell surface. The milk of cows and other animal species does not carry these protective sugar compounds. They are therefore sometimes added to baby milk powder products. It is assumed that these sugar molecules are able to prevent infection with BMMFs.

Literature:

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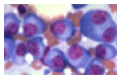
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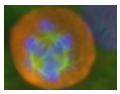
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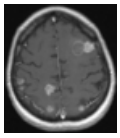
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