Casting out devils: How salmonella kills tumors

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Salmonella are regarded as bad guys. Hardly a summer passes without severe salmonella infections via raw egg dishes or chicken that find their way into the media. But salmonella not only harm us -- in the future they may even help to defend us against cancer. The bacteria migrates into solid tumors, and makes it easier to destroy them. Furthermore, in laboratory mice they independently find their way into metastases, where they can also aid clearance.

In the scientific journal *PLoS ONE*, Sara Bartels and Siegfried Weiss of the Helmholtz Centre for Infection Research (HZI) in Braunschweig, Germany now show how the bacteria migrate into tumours. A messenger substance from the immune system is the door opener: It makes blood vessels in the cancerous tissue permeable; enabling the bacteria to conquer and destroy the tumour. Simultaneously, blood streams from the vessels into the cancerous tissue, a so-called necrosis develops - and the tumour dies. "This influx of blood was the starting point for our investigations," says Siegfried Weiss, Head of the Molecular Immunology group at the HZI.

"There is an immunological messenger present during bacterial elicited inflammation that causes this kind of reaction. We searched for it - and found it." This messenger is named after its role in the immune system: tumour necrosis factor, TNF-alpha for short. Immune cells produce TNF-alpha when recognising salmonella, thus alarming other immune cells. This inflammatory reaction leads to an increased blood vessels permeability an action that also occurs in a tumour: TNF-alpha has an

easy task here because the blood vessels in cancer differ fundamentally from healthy arteries or veins. They are irregularly built, porous, partially with dead ends. A small amount of TNF-alpha is subsequently enough to dissolve the walls of the blood vessels in the tumour and allow the blood to stream into the cancerous tissue.

The scientists hope to be able to modify salmonella so they can be used in tumour therapy. The aim is for the bacteria to migrate specifically into tumours and cause them to die. The attractiveness of this way of destroying tumours is the lifestyle of salmonella. They can live almost everywhere, including tissues, which are badly supplied with blood and thus have hardly any oxygen supply. And it is precisely these areas that are scarcely reachable in a cancerous ulcer using common cancer therapies: chemotherapeutics cannot be transported to an area where there is no blood flow. And even radiation therapy requires oxygen for its reactions in the tissue.

The phenomenon of bacteria attacking tumours has been known to scientists for a long time. However, a cancer therapy with potential pathogens has been unthinkable before now. The risk of the patient dying due to an infection was too high. "We have obtained an important indication of how bacteria migrate into tumours. We can now try to manipulate these bacteria to use them in cancer therapy without causing deadly infections," says Sara Bartels.

The results of her study will be particularly helpful in this: she was able to show that the release of TNF-alpha plays a part in enabling salmonella to colonise the tumour efficiently. Subsequently, salmonella that is attenuated too strongly may no longer be able to migrate into the tumour because the immune system does not react properly and produces too little of the necrosis factor. "We need to find the right amount of bacteria aggressiveness, allowing the tumour to be colonised and destroyed without harming the patient," she says.

If the scientists succeed in accomplishing this feat, they may be able to take the next step forward: using salmonella to release therapeutic substances within the tumour and thus participate in its destruction. They could then penetrate deep within the tumour with the salmonella, reaching the very last cancer cells - a revolution in tumour therapy. "Our experiments are currently limited to absolutely basic research and experiments with laboratory mice," says Siegfried Weiss, "it may take years before this method is usable for human patients."

More information: Leschner S, Westphal K, Dietrich N, Viegas N, Jablonska J, et al. 2009 Tumor Invasion of Salmonellen enterica Serovar Typhimurium Is Accompanied by Strong Hemorrhage Promoted by TNF-alpha. PLoS ONE 4(8): e6692. doi:10.1371/journal.pone.0006692

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