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Molecular 'Signature' Protects Cells from Viruses

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Viruses are cunning little parasites: they breed by forcing the affected cells to do what they want. By fake commands they get them to produce new viruses. However, the cell often notices that there is something fishy going on. Researchers at the University of Bonn and Munich's Ludwig Maximilian University have now discovered why: cells are in a position to attach their 'signature' to their commands, whereas viruses cannot. Their findings are published on 12 October in the prestigious journal *Science*.

Every cell constantly produces a whole arsenal of proteins. The instruction what is to be built comes from the cell nucleus: this is where the DNA is stored, the heredity molecule in which, so to speak, the construction blueprints for all cellular proteins are stored. If a particular protein is to be produced, the appropriate command is 'copied' in the cell nucleus. The copy consists of a DNA-like substance, the RNA. Via pores in the cell nucleus it reaches the cell plasma. The individual parts of the desired protein are put together there on a kind of assembly line. In this process the assembly line follows exactly the blueprint which is stored in the relevant RNA.

This method has an Achilles heel: 'enemies' can misuse the assembly line to produce their own proteins by faking the commands. Viruses, for example, basically consist of a small protein capsule which surrounds its genetic make-up – usually an RNA molecule. This RNA mainly contains the blueprint for new capsule proteins. By injecting its RNA into the cell, the virus re-programmes it: the cell production line then produces

large numbers of new virus capsules. These are filled with virus RNA and attack more cells.

‘However, the cells are not completely at the mercy of a virus attack,’ Professor Gunther Hartmann, head of the Bonn University Clinic’s Department of Clinical Pharmacology. ‘They often recognise the alien RNA and set off the alarm: for example, they then produce what is known as the beta interferon, thereby activating specific killer cells. They also initiate the cell’s suicide programme – apoptosis. The viruses cannot then continue to breed.’

Up to now it was not known how cells distinguish their own RNA from that of the ‘enemy’. The latest findings, which a Japanese research team was also involved in, now shed light on the matter: they show that the instructions from the cell’s nucleus carry a kind of ‘signature’, which is missing in the virus commands. RNA is like a long string. In viruses there is a specific chemical signal, known as a triphosphate, located at one end of this string. The RNA in the cell’s nucleus basically also contains this triphosphate end. However, on top of it there is an additional short molecule, a molecular cap. ‘In all animals and plants the RNA which encodes proteins has this kind of molecular signature,’ Dr. Veit Hornung and Professor Stefan Endres of the Munich University Clinic’s Department of Clinical Pharmacology emphasise. ‘Apart from other functions it is also the signal that shows that the cell’s own RNA is involved.’

However, in all cells there are also RNAs which do not have a molecular cap. ‘Despite this they do not result in an immune reaction,’ Dr. Hornung says. ‘They sign their commands in a different way, viz. by means of a complex biochemical process which takes place in a special sub-structure of the cell’s nucleus, known as the nucleolus.’ These RNAs do not store information, being responsible for important tasks in ‘assembling’ the proteins.

The fact that RNAs without a ‘signature’ stimulate an immune reaction and initiate cell suicide opens up completely new perspectives for the therapy of virus infections and cancer cases: for example, RNA chains with a triphosphate end could be produced and fed into cancer cells. This could also trigger an anti-viral immune response. ‘Our findings are also important for gene therapy,’ Professor Hartmann stresses. ‘Before we attempt to cure diseases by introducing genetic material, we ought to understand precisely how the cells react to this genetic material.’

Source: University of Bonn