DESY X-ray source reveals decoy protein of a herpes virus at work

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With the help of DESY's X-ray source DORIS III, an international team of scientists decoded an important weapon used by a widespread human herpes virus. The study reveals at the molecular level how the Epstein-Barr virus (EBV) deactivates the alert system of the body's immune defence by using a molecular decoy. The analysis has implications on the development of new therapies and drug compounds, as the team led by Savvas Savvides from Ghent University (Belgium) and colleagues from the European Molecular Biology Laboratory (EMBL), Grenoble (France) and Hamburg (Germany), report in *Nature Structural & Molecular Biology*.

The Epstein-Barr virus is a member of the herpes virus family and can causes a range of diseases including the glandular fever (mononucleosis), also known as "kissing disease". Moreover, it plays a role in at least one type of cancer. The pathogen also labeled "human herpes virus 4" is extremely widespread, with 90 to 95 per cent of the adult population infected worldwide. Often, the infection is asymptomatic and the virus usually remains latent in the human body.

It was already known that the Epstein-Barr virus secretes a protein named BARF1 that blocks the protein hCSF-1 in the human body. hCSF-1 (human CSF-1) is a so-called growth factor which plays an essential role in the immune defence by stimulating the growth of white blood cells (leucocytes).

For the first time the scientists now shed light upon how the hCSF-1

blocking works at the molecular level. Using different methods at the European Synchrotron Radiation Facility ESRF, at the Swiss Light Source SLS and at Deutsches Elektronen-Synchrotron DESY the authors investigated the molecular structures of BARF1, hCSF-1 and the combination of the two. At the EMBL beamline X33 at DESY's particle accelerator DORIS III, it was also possible to elucidate the protein structure in solution to investigate the proteins under conditions closer to their natural environment.

The study showed that BARF1 surprisingly does not block the active binding site of hCSF-1, but catches the immune protein at a new spot instead, away from its cognate receptor-binding site. Each BARF1 toroid locks three copies of doubled hCSF-1 (dimers) and changes their shape, rendering them inactive. This way the virus prevents monocytes from maturing into macrophages, a key cell type in the immune response against viral and microbial infections.

"The discovered mechanism to modulate the immune response is really unique and probably the most exciting result of the study," said Dmitri Svergun who led the work at EMBL in Hamburg, that was partly funded by the SYNC-LIFE grant of the German Federal Ministry of Research (BMBF). In this highly interdisciplinary project, the work at Hamburg provided vital structural information about the relevant complexes in solution including a direct comparison of BARF1 structure before and after complexation with hCSF-1. "As the secretion of BARF1 is highly associated with types of carcinomas, understanding how BARF1 may interfere with the human immune response is crucial for shedding light on the process of the diseases and developing possible therapies," said Svergun.

"An equally exciting aspect of our work has been the unravelling of the way CSF-1 truly works," explained Savvides. "So by studying an inhibited form of CSF-1 we actually learned how it functions in a

cooperative manner with its cognate receptor." This has profound implications for the development of therapeutic approaches against CSF-1 signaling as such, an area of great clinical importance in its own right.

More information: "Allosteric competitive inactivation of hematopoietic CSF-1 signaling by the viral decoy receptor BARF1", Savvas N. Savvides et al., *Nature Structural & Molecular Biology*, DOI 10.1038/nsmb.2367

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