Bacterial protein found in the urogenital tract may contribute to reduced fertility, birth defects

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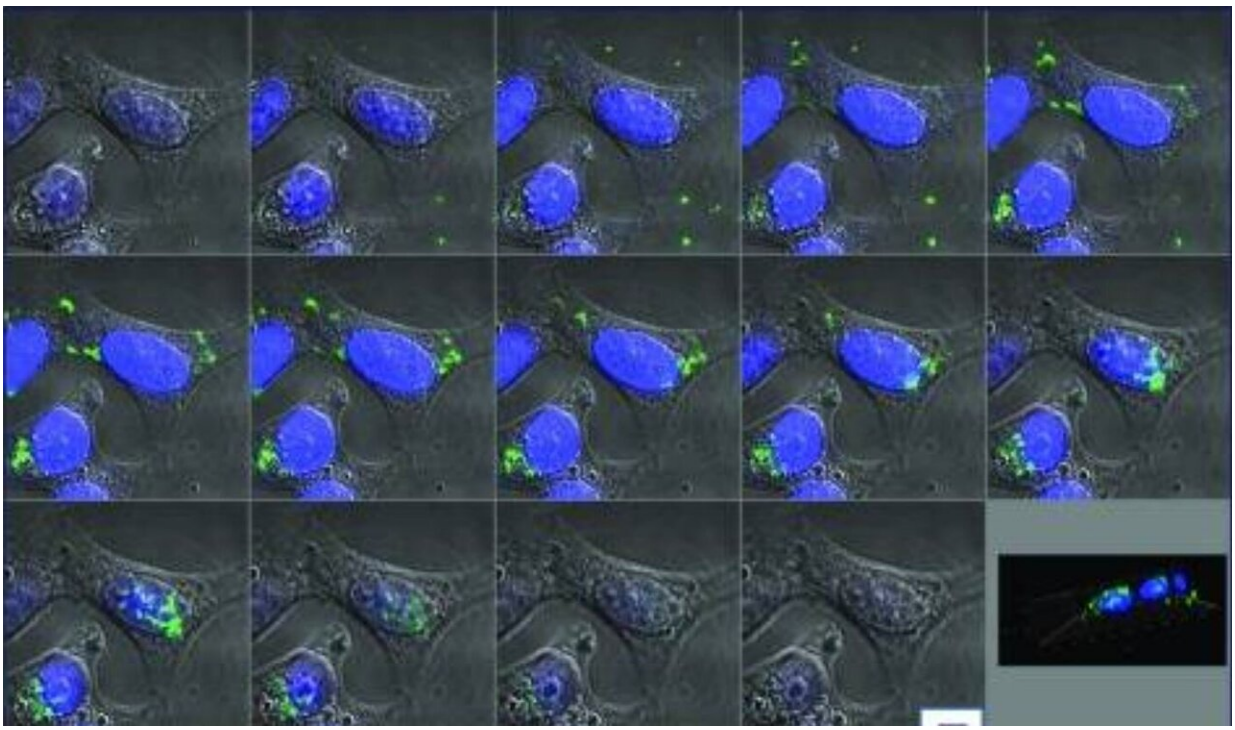

The bacterial protein DnaK (green) is taken up into human cancer cells and moves to the cell's nucleus (blue), where the DNA is located. Credit: PNAS 2018 Dec 18; 115(51): E12005–E12014.

A team of researchers from the University of Maryland School of Maryland's (UMSOM) Institute of Human Virology (IHV), a Center of

Excellence of the Global Virus Network (GVN), published new findings that emphasize the crucial role of the urinary and genital tract microbiota in adverse pregnancy outcomes and genomic instability that originate in the womb during fetal development.

The study, published on July 17 in the *Proceedings of the National Academy of Sciences (PNAS)*, established a new link between genomic instability and a protein from Mycoplasma fermentans, a kind of bacterium that commonly colonizes the urogenital tract. This bacterial protein also reduced fertility in mother mice and resulted in more birth defects in their newborn pups.

This research was spearheaded by Davide Zella, Ph.D., Assistant Professor of Biochemistry and Molecular Biology at UMSOM's IHV and Robert Gallo, MD, The Homer & Martha Gudelsky Distinguished Professor in Medicine, Co-Founder and Emeritus Director of UMSOM's IHV, and Co-Founder and Chair of the Scientific Leadership Board of the Global Virus Network.

"Our results not only broaden our understanding of the interplay between the urogenital tract microbiota and human reproductive health, but also shed light on the previously unidentified contribution of the human microbiota to genetic abnormalities," said lead author on the study Francesca Benedetti, Ph.D., Research Associate of Biochemistry and Molecular Biology in UMSOM's IHV.

"We aim to further explore the mechanisms underlying these findings and their potential implications for preventing and treating chromosomal abnormalities and genetic diseases," said co-lead author Giovannino Silvestri, Ph.D., former Research Associate of Medicine in UMSOM's IHV.

The human microbiota is known to affect metabolism, susceptibility to

infectious diseases, immune system regulation, and more. One of these bacterial components, Mycoplasmas, have been linked to various cancers.

The research team has been studying one Mycoplasma protein, DnaK, which belongs to a family of proteins that safeguards other bacterial proteins against damage and aids in their folding when they are newly made, acting as a so-called "chaperone." However, while this protein is advantageous for bacteria, its effects on animal cells are less favorable.

To this regard, the team had previously demonstrated that this DnaK is taken up by the body's cells and it interferes with key proteins involved in preserving DNA integrity and in cancer prevention, such as the tumor suppressor protein p53.

For this latest study, researchers created mice that make the DnaK protein normally produced by the bacterium Mycoplasma fermentans. These mice with exposure to DnaK accrued genomic instability in which entire sections of the genome were duplicated or deleted, resulting in mice with varying numbers of copies of certain genes.

The team noticed that some of these mice from three to five weeks of age had problems with movement and coordination. They found that these mice have a deletion in the Grid2 gene, which in humans leads to the rare genetic disease known as spinocerebellar ataxia-18 (SCAR18) that causes delayed development of skilled movements and intellectual disabilities.

"Remarkably, this instance marks the first time a mouse model successfully recapitulated a human genetic disease de novo, showcasing this model's potential for further cancer biology research," said Dr. Zella.

More than a third of the female mice that made the DnaK protein were unable to get pregnant. Additionally, more than 20% of the pups born from moms with the DnaK protein had some sort of birth defect/deformity.

"The occurrences of genomic instability, in the form of increased number of copy number variations, could explain the decreased fertility and the increased instances of abnormally developed fetuses we observed upon DnaK exposure," said Dr. Gallo.

"These data build upon our initial work which discovered the disruptive role of DnaK on key proteins involved in the proper repair of damaged DNA, which are also known to play a role in the onset of copy number variations. Our ongoing commitment is to better understand the potential implications of these findings in cellular transformation and cancer."

UMSOM Dean Mark T. Gladwin, MD, who is also Vice President for Medical Affairs, University of Maryland, Baltimore and the John Z. and Akiko K. Bowers Distinguished Professor, commended the work. "The researchers raise a significant question regarding whether DnaK can interfere with fetal development in humans. An important next step would be to investigate whether neutralizing either the bacteria or this protein could preserve fertility and prevent certain birth defects," he said.

More information: Benedetti, Francesca et al, Mycoplasma DnaK increases DNA copy number variants in vivo, *Proceedings of the National Academy of Sciences* (2023). DOI: 10.1073/pnas.2219897120

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