Molecules produced by cells in response to stress may be indicators of disease

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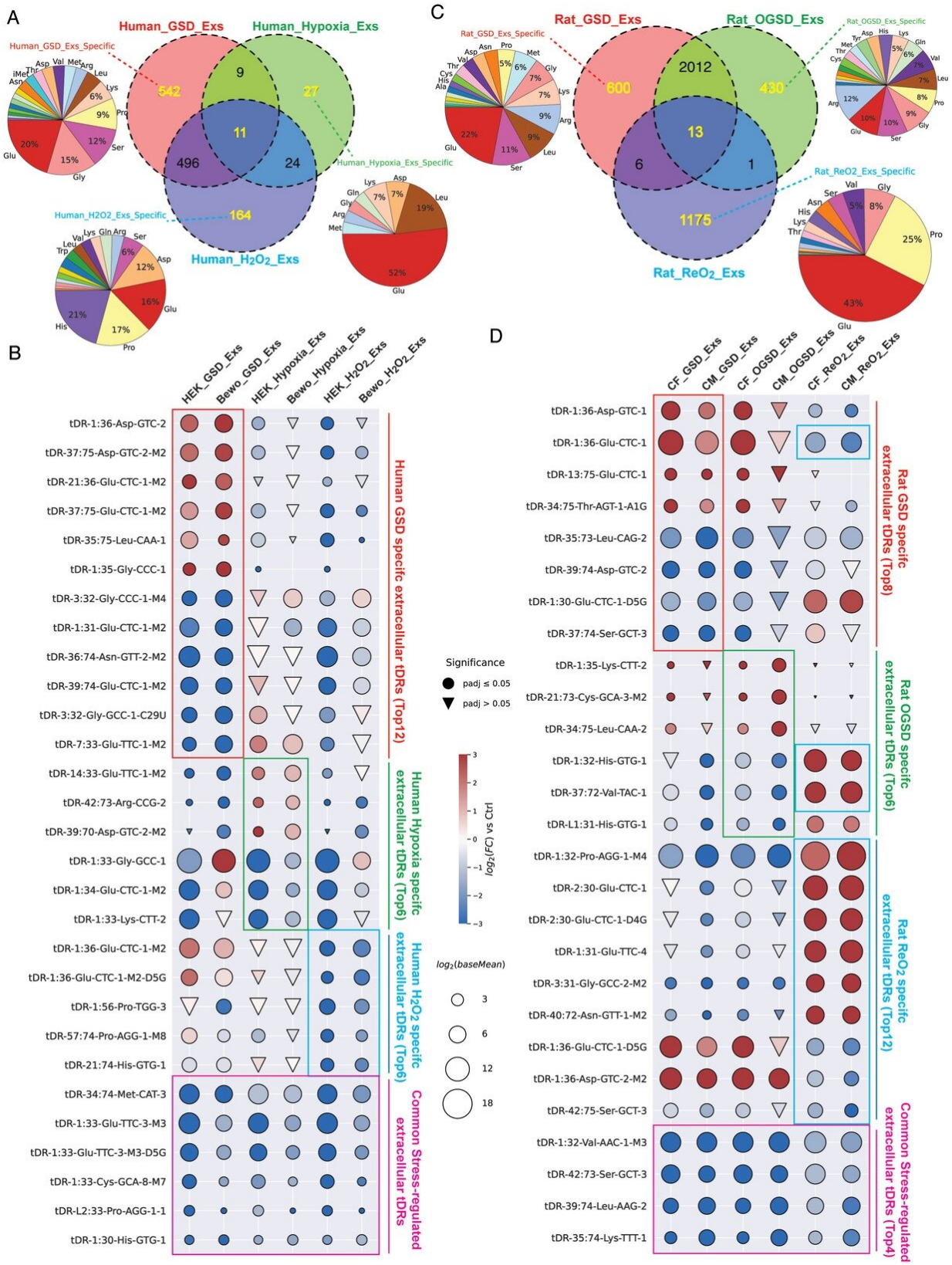
A
Human_GSD_Exs
Human_Hypoxia_Exs
Human_H2O2_Exs
542
9
27
11
496
24
164
Human_GSD_Exs_Specific
Human_Hypoxia_Exs_Specific
Human_H2O2_Exs_Specific
C
Rat_GSD_Exs
Rat_OGSD_Exs
Rat_ReO2_Exs
600
2012
430
13
6
1
1175
Rat_GSD_Exs_Specific
Rat_OGSD_Exs_Specific
Rat_ReO2_Exs_Specific
B
HEK_GSD_Exs
Bewo_GSD_Exs
HEK_Hypoxia_Exs
Bewo_Hypoxia_Exs
HEK_H2O2_Exs
Bewo_H2O2_Exs
Human GSD specifc extracellular tDRs (Top12)
Human Hypoxia specifc extracellular tDRs (Top6)
Human H2O2 specifc extracellular tDRs (Top6)
Common Stress-regulated extracellular tDRs
Significance
padj ≤ 0.05
padj > 0.05
log2(FC) vs Ctrl
log2(baseMean)
D
CF_GSD_Exs
CM_GSD_Exs
CF_OGSD_Exs
CM_OGSD_Exs
CF_ReO2_Exs
CM_ReO2_Exs
Rat GSD specifc extracellular tDRs (Top8)
Rat OGSD specifc extracellular tDRs (Top6)
Rat ReO2 specifc extracellular tDRs (Top12)
Common Stress-regulated extracellular tDRs (Top4)

Specific and shared extracellular tDR signatures among three profiled stressors. A) Numbers of the specific and shared extracellular tDRs altered by three profiled stressors in HEK and BeWo cell-derived Exs and their parent tRNA isotype distribution. B) The most significantly regulated extracellular tDRs that were specifically for GSD, hypoxia, and H_2O_2, and were shared among three stressors in HEK and BeWo cell-derived Exs. C) Numbers of the specific and shared extracellular tDRs altered by three profiled stressors in CF and CM cell-derived Exs and their parent tRNA isotype distribution. D) The most significantly regulated extracellular tDRs that were specifically for GSD, OGSD, and ReO_2, and were shared among three stressors in CF and CM cell-derived Exs. Credit: *Advanced Science* (2022). DOI: 10.1002/advs.202200829

The body's ability to respond to various types of stress is essential for maintaining health, and failure of such adaptive stress responses can trigger or worsen numerous diseases. New research led by investigators at Massachusetts General Hospital (MGH) and published in *Advanced Science* reveals that cells often release certain RNA molecules called tDRs in response to stressors, and that different tDRs may serve as markers of cellular stress in different diseases.

"RNA molecules have long been known to be the messenger between DNA (the genetic code) and proteins (the functional molecules of the cell); however, the past decade has seen investigators discover new functions of RNAs that do not translate into proteins—the so-called non-coding RNAs," says senior author Saumya Das, MD, Ph.D., co-director of the Resynchronization and Advanced Cardiac Therapeutics Program at MGH.

Das notes that there's a growing list of non-coding RNAs with diverse functions, and among these, a new class of RNAs has been found to arise from so-called transfer RNAs that normally function to help make proteins from classic messenger RNAs. These RNAs, called tRNA-

derived small RNAs (tDRs), appear to be generated when larger "parent" tRNAs are cut into smaller versions by stress-activated enzymes.

By studying a variety of human and rat cells under three stressors—nutritional deprivation, low oxygen and oxidative stress—that are often present in many disease states, Das and his colleagues generated a comprehensive landscape of tDRs that can be found inside cells (cellular) and outside cells (extracellular) during different stress responses. They also found that key proteins called RNAses are important for the generation and stability of extracellular tDRs.

"While tDRs play important roles in cellular functions, we have also found that tDRs are released by cells where they may serve as markers of cellular stress in different diseases," says lead author Guoping Li, Ph.D., an instructor in medicine at MGH and Harvard Medical School. "We saw that different types of stress signals can affect the cellular and extracellular tDRs in different types of cells, and that there are 'signatures' of these stress signals."

The team created an atlas of the stress signatures for both cellular and extracellular tDRs that can be used not only as indicators of disease but also as a starting point for scientists who are interested in studying the roles of distinct tDRs in cancer, fibrosis, and other conditions. Das and colleagues are focusing on one such tDR and its role in kidney disease.

More information: Guoping Li et al, Distinct Stress-Dependent Signatures of Cellular and Extracellular tRNA-Derived Small RNAs, *Advanced Science* (2022). DOI: 10.1002/advs.202200829

Provided by Massachusetts General Hospital

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