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Coping with stress: Lessons from yeast

Yeast cells subjected to many different stresses elicit an acute transcriptional stress response mediated by the Msn2 transcription factor, which alters expression of both a stress specific cohort of genes as well as a common cohort of genes that changes expression in a stereotypic fashion upon exposure to any of a wide variety of stresses. We have shown by dynamic single cell analysis that stresses regulate Msn2 activity through cytoplasmic to nuclear relocalization but do so in an unusual way: stresses induce increased frequency of bursts of short-lived, recurrent periods of Msn2 nuclear localization with different stresses eliciting different patterns of bursts. Moreover, genetically identical cells subjected to an identical stress can behave quite differently. We have proposed that this idiosyncratic behavior allows populations of cells to "hedge their bet" as to what will be the optimal strategy for surviving ensuing stress. We have used computational modeling and single cell analysis to determine that bursting is a consequence of the noise in the stress signaling pathways, amplified by the small number of Msn2 molecules in the cell. Moreover, we have applied genome wide chromatin immunoprecipitation and nucleosome profiling to address how different stresses determine where Msn2 binds under a particularly stressful condition and thus what genes are regulated by that stress and how that binding affects and is affected, by nucleosome positioning and other transcription factor binding. These results provide an *in vivo* validation of indirect cooperativity of transcription factor binding, mediated by partial unwinding of nucleosomes by one transcription factor to allow access for a second transcription factor to a previously occluded binding site. Finally, we have addressed the "bet hedging" hypothesis by showing that persistence of the Msn2-mediated stress response yields cell growth arrest and have identified the targets responsible for that growth arrest. We have applied experimental evolution paradigms to address the relative fitness of cells exhibiting stochastic stress response versus those with a uniform response. In short, our results indicate that the stress response is complex and that complexity is critical for cell survival.

Speaker Biography

James R Broach is a distinguished Professor and Chair of the department of Biochemistry and Molecular Biology at Penn State College of Medicine, Director of the Institute for Personalized Medicine. He was Professor of molecular biology at Princeton University from 1984-2012, where he served as an Associate Director of the Lewis Sigler Institute for Integrative Genomics and Co-Director of the Center for Computational Biology. He has served as Chair of the Genomics, Computational Biology and Technology Study Section at NIH as well as Chair of Numerous Special Emphasis Genomics Panels. He was Co-Founder and Director of Research for Cadus Pharmaceuticals from 1992 to 2000. He is a Fellow of the American Academy of Microbiology and of the American Association for the Advancement of Science. He has published more than 175 articles in the area of Molecular Biology and Genomics and holds a number of patents in Drug Discovery Technologies.

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