Cell biology of disease and aging: a two-way street

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The Cellular Mechanisms of Disease and Aging Minisymposium featured studies investigating human disease and aging in a wide variety of model systems. Four talks highlighted disease mechanisms. **Benoît Renvoisé** (National Institutes of Health) described a mouse model for Troyer syndrome (SPG20), an autosomal recessive hereditary spastic paraplegia. *Spg20*$^{-/-}$ knockout mice lacking the spartin protein showed gait deficits. Spartin interacts with various proteins, including the ESCRT-III subunit IST1 and several E3 ligases; neurons and fibroblasts cultured from these mutant animals demonstrated roles for spartin in endocytic sorting, cytokinesis, and lipid droplet turnover.

R. Claudio Aguilar (Purdue University) discussed the oculo-cerebral-renal syndrome of Lowe, a rare X-linked disorder characterized by cataracts, learning disabilities, and renal dysfunction. The Lowe syndrome protein Ocrl1 was identified years ago, but the disease's pathogenesis has remained unclear. In an impressive range of experimental systems, including zebrafish and patient-derived cells, Aguilar showed that Ocrl1 was important for primary cilia assembly, indicating that Lowe syndrome is a "ciliopathy." Mechanistically, Ocrl1 is involved in endocytic and secretory trafficking to cilia in a Rab8-, Appl1-, and IPIP27/Ses-dependent manner.

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James Shorter (University of Pennsylvania) discussed amyotrophic lateral sclerosis, a severe neurodegenerative disorder affecting upper and lower neurons, as well as frontotemporal dementia. Studies of both familial and sporadic forms of these disorders have established key roles for RNA-binding proteins TDP-43 and FUS, and Shorter's group used protein biochemistry and *Saccharomyces cerevisiae* as a model system (in collaboration with Aaron Gitler) to define mechanisms responsible for the misfolding and toxicity of TDP-43 and FUS. They identified novel prion-like domains required for aggregation in both proteins, and their bioinformatic analyses identified other candidate genes for these disorders, including TAF15.

Huntington Potter (University of South Florida) and colleagues had earlier shown that chromosome missegregation and aneuploidy are induced in Alzheimer's disease models by mutant forms of amyloid precursor protein and presenilins and their product, Aβ. Their recent studies in somatic cells and *Xenopus* egg extracts demonstrate that Aβ impairs assembly and maintenance of the mitotic spindle, possibly due to Aβ's inhibition of mitotic motor kinesins. Such disruption may dysregulate forces governing the spindle, causing defective mitotic structures. Resulting impairments in neurogenesis may explain why aneuploid/hyperploid neurons are prone to degeneration in Alzheimer's disease.

The final presentations emphasized aging—a progressive failure of cellular processes and a risk factor for many disorders. **Gabrielle Boulianne** (Hospital for Sick Children) described the crucial role played by the protein GnT1, which is required for paucimannose *N*-glycan synthesis in *Drosophila*. Rescue of null flies resulted in an unexpectedly dramatic increase in life expectancy (127 days vs. 54 days for wild-type), with increased oxidative stress resistance.

Finally, **Coleen Murphy** (Princeton University) described the early aging phenotype of female reproductive cessation due to declined oocyte quality. Using DNA microarrays, she uncovered a distinctive genetic signature for aging oocytes that emphasizes DNA integrity and cell cycle control and is reversed in insulin and TGF-β mutants. This signature is strikingly distinct from the bias toward maintenance of protein and cell quality seen in somatic aging.

Despite the wide variety of cellular systems and diseases discussed, a unifying theme was the importance of a two-way street linking basic cell biology with disease and aging. Cell biological investigations are crucial for understanding disease pathogenesis and aging. At the same time, disease-related studies, buttressed by dramatic advances in mining the genetic underpinnings of disease, increasingly lead to fundamental insights in basic cell biology.