Connecting the plasma membrane to the nucleus by intermediate filaments

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Talks at the Minisymposium on "Intermediate Filaments from Cytoplasm to Nucleus" demonstrated the structural and functional diversity of intermediate filaments (IFs) and their multiple binding partners and highlighted their importance in both cellular mechanics and gene regulation.

Toward a better characterization of IF networks

The IF gene superfamily encodes >50 different proteins that assemble into distinct, nonpolar supramolecular structures in the cytoplasm and the nucleus (Herrmann and Aebi, 2016). The composition of the IF network varies not only among cell types but also during cell differentiation and pathological conditions such as cancer development. Shedding further light onto the diversity of IF filaments, **Mikaela Wiking** (Lundberg laboratory, SciLifeLab, Sweden) cataloged expression of IFs and associated proteins in >40 different human cell lines. The results, which are part of the Human Protein Atlas Project (www.proteinatlas.org), reveal several previously uncharacterized IF-associated proteins, with distinct cell–type specific expression and subcellular localization.

IFs in cell mechanics and migration

Whereas IFs, actin, and microtubules form distinct cytoskeletal filament systems, increasing studies point to a dynamic interplay between these networks in motile cells (Leduc and Etienne-Manneville, 2015). **Sandrine Etienne-Manneville** (Institut Pasteur-CNRS, France) showed that the turnover of vimentin, glial fibrillary acidic protein (GFAP), and nestin IFs in astrocytes involves actin-dependent retrograde flow and microtubule-dependent transport. As astrocytes start to migrate, the polarized reorganization of the IF network is triggered by a signaling cascade involving the small GTPase Cdc42, which increases kinesin-dependent anterograde transport while inhibiting the dynein-dependent retrograde transport of IF subunits. IFs, which provide structural support for cells, play a major role in the cell's responses to external mechanical forces. **Sachiko Fujiwara** (Mizuno laboratory, Tohoku University, Japan) showed that tensional force-induced reinforcement of actin stress fibers requires the interaction of the RhoA-targeting Rho-guanine nucleotide exchange factors Solo/ARHGEF40 with keratin IFs to activate RhoA signaling, which promotes stress fiber formation and keratin network organization. Further illustrating the importance of keratins in enabling cells to adapt to mechanical stress, **Joshua Broussard** (Green laboratory, Northwestern University) showed that interaction of desmoplakin with keratin filaments at desmosomes supports intercellular force transmission, traction force generation, and cell stiffness.

During in vivo migration, cells must squeeze through tight spaces. The nucleus, which is stiffer than the rest of the cytoplasm, can stall cell migration in dense extracellular environments (McGregor *et al.*, 2016). **Jan Lammerding** (Cornell University) showed that decreased expression of lamin A/C in breast cancer cells correlates with increased nuclear deformability and enhanced cell migration in confined environments. Furthermore, migration-induced nuclear deformation caused transient nuclear envelope rupture and DNA double-strand breaks (Denais *et al.*, 2016). **Ved Sharma** (Condeelis laboratory, Albert Einstein College of Medicine) found that the LINC complex, which connects the nucleus to the cytoskeleton, is crucial when cells migrate on microfabricated fibers that mimic the tumor microenvironment (Sharma *et al.*, 2014). LINC complex disruption altered nuclear shape and increased both cell speed and persistence in one-dimensional but not two-dimensional migration.

IFs control gene expression

Lamin IFs are the main components of the nuclear lamina, which interacts with chromatin and numerous transcriptional regulators (Osmanagic-Myers *et al.*, 2015). **Josette Northcott** (Weaver laboratory, University of California, San Francisco) found that elevating extracellular matrix stiffness to levels found in breast cancer tissue in three-dimensional culture of breast epithelial cells altered the expression of nuclear lamins and induced gene expression changes. Of interest, differentially expressed genes were particularly enriched for those contained in lamina-associated domains. **Georg Weitzer** (Medical University of Vienna, Austria) presented the unexpected discovery that the muscle-specific IF desmin can localize to the nucleus and regulate gene expression during cardiomyogenesis. At the early stage of cardiomyogenesis, desmin did not form filaments but was found in the nucleus of a significant fraction of cardiac stem cells, where it activated transcription of the Nkx2.5 transcription factor, a key regulator of cardiac development, and its downstream genes.

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Structural organization of lamin networks

Although the assembly of cytoplasmic IF proteins into filaments is well established (Herrmann and Aebi, 2016), the organization of lamins into nuclear IFs and the lamina network is incompletely understood. Studying the in vitro assembly of a panel of progressively trimmed lamin constructs, **Harald Herrmann** (German Cancer Research Center, Germany) established the minimal criteria for longitudinal and lateral assembly of lamin dimers into head-to-tail polymers and higher-order structures, as well as the effect of disease-causing lamin mutations on assembly. **Ohad Medalia** (University of Zurich, Switzerland) showed stunning images of the nuclear lamina in somatic cells reconstructed from cryo–electron tomography. Surprisingly, both A-type and B-type lamins formed filaments only 3.5 nm in diameter, suggesting that the filaments are composed of longitudinal, overlapping tetramers.

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