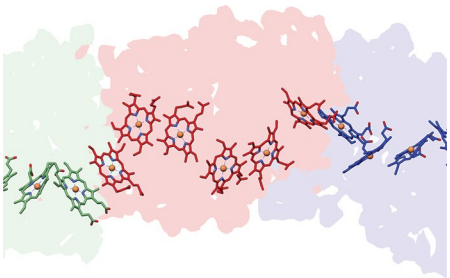
STRUCTURAL BIOLOGY

The new face of nanowires

Cell **177**, 361–369 (2019)



Credit: Elsevier

The common soil bacterium *Geobacter sulfurreducens* forms filamentous appendages that function as nanowires to enable long-range electron transfer during respiration and to exchange electrons with other species. Multiple previous biochemical and imaging studies have proposed that these nanowires were type IV pili consisting of the protein PilA. Using a combination of cryo-EM, mass spectrometry and electronic conductivity on isolated filament proteins, Wang and Gu et al. now identify the nanowires as polymerized filaments of the cytochrome OmcS instead. The heme cofactors in the OmcS nanowires form a continuous chain of parallel-stacked pairs, which optimizes electron transport along the chain and may also enhance stability at the protein–protein interfaces between OmcS units. Although cytochrome polymerization up to tetramers has been observed in other systems, the micrometer scale of the OmcS nanowires, each consisting of hundreds of cytochrome proteins, is unexpected. These nanowire structures shed new light on how bacteria mediate electron transfer during various processes and prompt new investigation into a potential regulatory, rather than structural, role of PilA in this system. *CD*

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TRANSCRIPTIONAL REGULATION

From outside to inside

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The insulin receptor (IR) plays critical roles in normal physiology and multiple chronic diseases through binding insulin and transducing this extracellular signal into cells as a tyrosine kinase. Although the presence of IR in the nucleus has been reported, little is known about its potential targets and biological function. Hancock et al. reported that IR at the cell surface could translocate into the nucleus upon insulin stimulation. There it forms a complex with RNA polymerase II and other factors involved in transcription to regulate the expression of genes related to insulin function. Further studies found that the association of IR with chromatin was mediated by a transcription co-regulator, host cell factor-1 (HCF-1). Knockdown of HCF-1 impaired the interaction of IR with chromatin and downstream gene expression without affecting the canonical PI3K-Akt cascades mediated by the tyrosine kinase activity of membrane-localized IR. HCF-1 knockdown mice phenocopied the effects of IR deficiency on lipid metabolism, suggesting a major role of nuclear IR in metabolic regulation. These findings reveal a new pathway for insulin signaling and add another layer of complexity to transcriptional regulation mediated by IR. *YS*

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ION CHANNELS

Arrestin-g pain

Sci. Signal. **12**, eaav0711 (2019)

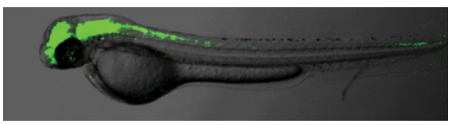
Injury invokes signaling pathways leading to inflammation and pain modulation (antinociception) that accompany tissue healing. At sites of inflammation, antinociception is generated via endogenous opioids that act through the GPCR MOR in pain-sensing fibers (nociceptors). Meanwhile, TRPV1 channels also found in nociceptors respond to inflammatory mediators and acutely contribute to pain hypersensitivity. Aiming to understand this interplay between inflammation and opioid analgesia and to define the role of TPRV1 in opioid-induced antinociception, Basso et al. found that activation of TRPV1 diverts the GPCR effector β-arrestin2 to the nucleus coincident with enhanced MAPK signaling. When β-arrestin2 is physically separated from cell membrane MOR, the receptor does not bind β-arrestin2 or become internalized for desensitization and recycling. Using a mouse model of chronic inflammatory pain as well as morphine-treated mice, the authors found that TRPV1 knockout blunted endogenous opioid analgesia and led to peripheral opioid desensitization. These results suggest that TRPV1, through its effects on β-arrestin2 traffic, enhances analgesia while maintaining peripheral opioid receptor function and that the interplay between TRPV1 and β-arrestin2 may contribute to the transition from acute to chronic pain. *MB*

https://doi.org/10.1038/s41589-019-0300-z

HOST–PATHOGEN INTERACTIONS

Lipids for life

PLoS Pathog. **15**, e1007597 (2019)



Credit: PLoS

During microbial infection, inflammatory lipids such as eicosanoids are generated by host macrophages to kill invading pathogens. The fungus *Cryptococcus neoformans* produces eicosanoid species that are indistinguishable from their vertebrate counterparts, and an eicosanoid-deficient *C. neoformans* strain (*Δplb1*) has less robust growth and survival within host macrophages in vitro, suggesting that the fungus disrupts host eicosanoid signaling to promote its growth. In support of this model, Evans et al. found that addition of exogenous prostaglandin E2 (PGE_2) could recover the intracellular proliferation of the *Δplb1* mutant and enhance the virulence of this mutant in a zebrafish infection model. This activity required the dehydrogenated form of PGE_2, 15-keto-prostaglandin E_2. While knockout of the *C. neoformans* PGE_2 biosynthetic enzyme limited *C. neoformans* growth in vitro or in vivo, inhibition and knockdown of host prostaglandin synthesis had no effect. The authors further found that the growth of *C. neoformans* during infection required activation of the host nuclear receptor PPAR-γ with 15-keto-PGE_2 as the agonist. These results suggest that *C. neoformans*-derived PGE_2 is converted to 15-keto-PGE_2 to activate host PPAR-γ, thereby manipulating host immunity to promote its own growth. *MB*

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