Nature Reviews Molecular Cell Biology | Published online 2 Dec 2015; doi:10.1038/nrm.2015.9

Journal club

CELL BIOLOGY TO DISEASE AND BACK

Three related classic cell biology papers, published in 1991, had a huge positive impact on the field of cell biology and far beyond. Two of these papers elegantly showed that mutations in keratin 14 (Coulombe *et al.*, cited >480 times; Bonifas *et al.*, cited >320 times) cause the blistering skin disease epidermolysis bullosa simplex (EBS). Prior to this, the function of the >70 intermediate filament proteins was poorly understood. Furthermore, no direct disease connection was known for any intermediate filament protein, except for that published in the earlier 1991 paper (Vassar *et al.*), which found a blistering skin phenotype (similar to human EBS) in transgenic mice expressing keratin 14 with a carboxy-terminal deletion. This was the impetus for Pierre Coulombe (at the Fuchs laboratory) to search for keratin mutations in patients; the Bonifas study was based on classic genetic linkage analysis. Another major implication of these studies was the elucidation of mechanical cytoprotection as an important function of keratins and other intermediate filament proteins.

> “mutations in intermediate filament genes cause or predispose to > 70 distinct human skin, cardiac, neuronal, liver, premature ageing, ocular and metabolic diseases”

The success of using the keratin 14 transgenic mice led us to show in 1995 that the expression of a keratin 18 point mutation in mice, which is identical to the keratin 14 mutation in EBS patients, causes profound predisposition to liver injury, which we then validated in human studies. We further showed that keratin functions extend to non-mechanical roles. Similarly, other laboratories generated mouse models or examined humans directly, to show that mutations in intermediate filament genes cause or predispose to >70 distinct human skin, cardiac, neuronal, liver, premature ageing, ocular and metabolic diseases.

So what is next? Cell biology helped to unfold the causes of a range of human diseases, but now we need to circle back to the bench to develop cures for the broad array of intermediate filament-related diseases known as IF-pathies.

M. Bishr Omary
Department of Molecular and Integrative Physiology, Department of Medicine, University of Michigan, Ann Arbor, Michigan 48109, USA.
Correspondence to mbishr@umich.edu

The author declares no competing interests.

ORIGINAL ARTICLES Coulombe, P. A., *et al.* Point mutations in human keratin 14 genes of epidermolysis bullosa simplex patients: genetic and functional analyses. *Cell* **66**, 1301–1311 (1991) | Bonifas, J. M., *et al.* Epidermolysis bullosa simplex: evidence in two families for keratin gene abnormalities. *Science* **254**, 1202–1205 (1991) | Vassar, R., *et al.* Mutant keratin expression in transgenic mice causes marked abnormalities resembling a human genetic skin disease. *Cell* **64**, 365–380 (1991) | Omary, M. B. “IF-pathies”: a broad spectrum of intermediate filament-associated diseases. *J. Clin. Invest.* **119**, 1756–1762 (2009)