Nature Reviews Molecular Cell Biology | https://doi.org/10.1038/s41580-021-00369-3 | Published online: 08 April 2021

Journal Club

CELL SIGNALLING

THE BACTERIAL SOCIAL NETWORK AND BEYOND

Cellulose is the planet's most abundant biological polymer, but no one could have predicted that studies of cellulose synthesis regulation in bacteria would lead to the discovery of a ubiquitous bacterial signalling molecule: cyclic-di-GMP (c-di-GMP). This eventually changed our perception of bacteria as solitary cells and launched a thousand ships to understand garrulous 'multicellular' bacterial communities. It also illustrated how any group of cells might send signals to alter the microenvironment and to function cooperatively.

This story began with the search for cellulose synthases in *Acetobacter xylinium*. It became clear that some other enzymatic activity in bacterial membranes was required for full cellulose synthase activity. Chance findings indicated that non-hydrolysable GTP molecules weakly activated cellulose synthases. In a heroic effort, Benziman and colleagues purified the molecule that fully stimulated cellulose synthesis, and with elegant biochemical approaches inductively deduced that this molecule was made of two GMPs, connected by a 3′–5′ phosphodiester bond (c-di-GMP).

These findings enabled Benziman's subsequent discoveries of new diguanylate cyclase and diesterase families, and transformed our view of 'unicellular' signalling and lifestyles. We recognized that bacteria use novel cyclic nucleotides to relay intracellular signals in order to alter the 'community' microenvironment. The paper pithily concludes: "Although the regulation of cellular synthesis has been demonstrated only for *A. xylinum* it is tempting to speculate that mechanisms similar to that described here, based on cyclic diguanilic acid or on related cyclic di or oligonucleotides may function in other organisms and other cellular processes." Only rarely have statements in manuscripts been this prophetic. It took 25 more years for a similar molecule to be found in mammals, cGAMP, which has a central role in immune cell function.

> These findings enabled Benziman's subsequent discoveries of new diguanylate cyclase and diesterase families, and transformed our view of 'unicellular' signalling and lifestyles

This concise manuscript exemplifies perseverance, chance, inductive deduction and the value of biochemistry. It has been 35 years since c-di-GMP was discovered, and this landmark paper, initially ignored, has now been cited over a thousand times. Benziman findings were dismissed as mere biochemical curiosities. Benziman died in 2003 — sadly before we awoke to the fact that c-di-GMP signals biofilm formation, motility, differentiation, virulence and the cell cycle across the bacterial kingdom, and that similar molecules exist in all cells. This discovery marked a turning point in microbiology and also paved the way to a universe of cosmopolitan cell communities.

Sunil Laxman
Institute for Stem Cell Science and Regenerative Medicine (inStem), Bangalore, India
e-mail: sunil@instem.res.in

ORIGINAL ARTICLE Ross, P. H. et al. Regulation of cellulose synthesis in *Acetobacter xylinum* by cyclic diguanylic acid. *Nature* **325**, 279–281 (1987)