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The first demonstration of the existence of reverse transcriptases in bacteria

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The central dogma in molecular biology is that DNA is the basic building block, carrying all genetic information from which mRNA is transcribed to produce proteins. However, this central dogma was challenged by the discovery of reverse transcriptases in 1970 by Baltimore (1970) and Temin (Temin and Mizutani, 1970). They studied how RNA tumor viruses were able to stably transform cells without using a DNA copy of the RNA viruses. They found that DNA was synthesized directly from viral RNA, leading to the discovery of RNA-dependent DNA polymerases. In other words, this enzyme is able to carry out the reverse reaction of RNA synthesis from DNA to synthesize DNA from RNA. Thus, this enzyme was termed a reverse transcriptase. This discovery was quite sensational then as it was against the central dogma of molecular biology. However, this is a good example of how thinking outside the norm can lead to a big breakthrough in science. The discovery of reverse transcriptases also raised an intriguing question on the origin of life, RNA first or DNA first. If RNA was first, it had to be reverse-transcribed into DNA to maintain the current form of life on earth. However, since the discovery of reverse transcriptases in animal viruses by Baltimore, Temin and Mizutani in 1970, it had been long thought that reverse transcriptases are unique to eukaryotes and do not exist in prokaryotes. However, through our research on a peculiar single-stranded DNA called msDNA found in *Myxococcus xanthus* (Yee et al., 1984; Furuichi et al., 1987a and b), we predicted that the biosynthesis of msDNA had to be carried out by a reverse transcriptase (Dhundale et al., 1987).

In 1988, our experiments found that msDNA is indeed synthesized by a reverse transcriptase and subsequently, we wrote three papers on our findings, one of which was submitted to Science on December 27, 1988 and the remaining two to Cell on January 26, 1989. To our surprise, Ben Lewin, the chief editor of Cell, called me while I was attending a meeting in San Francisco, urging me to withdraw the paper submitted to Science and resubmit it to Cell. He was very persuasive, promising me that all three papers would be immediately published back to back in one issue (I am not sure if Cell has ever published three papers by the same authors in a row in the same issue). I also received the following letter from him, written on December 1, 1988;

Dear Dr. Inouye,
I understand that you have evidence for the involvement of reverse transcriptase in the generation of msDNA (as predicted in your last manuscript). I am writing to say that I hope you will offer us the opportunity to consider the work for Cell to follow our earlier publications of the data on this interesting system.
Yours sincerely,
BL (signature)

In my long scientific career, this is truly the only time that I was persuaded by an editor of one of the major scientific journals to submit a paper on our findings to them, although our papers have been rejected many times by these journals including Cell. It was also the only experience for me to turn down the offer from a journal. This led to a serious concern that the two papers then already submitted to Cell might be rejected as a result of our not complying to their request. In addition, I might have ended up with no publications if the paper submitted to Science was also rejected. The reasoning behind rejecting Lewin's attractive offer was partially because of my pride and not wanting to bend to the will of a publication but mostly because of my strong confidence in our unprecedented discovery. My fear that all three papers would be rejected for publication was soon allayed, as all three papers were soon accepted. Cell and Science both competed to be the first to publish these papers but all three papers were published on the same day, February 24, 1989 (Inouye et al., 1989; Lampson et al., 1989a and b). The two Cell papers were actually published less than a month after the papers were received by the journal, as the papers were received by Cell on January 26, 1989. In the same year, Lim and Maas of New York University found that *E. coli* B also produces msDNA, and demonstrated that a reverse transcriptase is required for its synthesis. Their paper was published contiguously with our papers in the same issue of Cell (Lim and Maas, 1989).

The function of msDNA has yet to be elucidated even 30 some years after its discovery. However, recently, the overproduction of msDNA in *E. coli* was reported to cause a higher mutation rate and higher expression of ten proteins, most of which are associated with the dissimulation of various carbon sources (Jeong and Lim, 2004). It has been also reported that deletion of the gene for a retron reverse transcriptase in *Salmonella*