MILESTONE 6

Southern migration

DOI:
10.1038/nrg2244

It was a simple but clever idea that, in 1975, led Edwin Southern to invent a method that carries his name and that has revolutionized the study of DNA.

In the early 1960s, Julius Marmur and Paul Doty published a study that accurately described the conditions for the optimal renaturation of DNA complementary strands, upon denaturation by high temperatures. They proposed that high temperature was required to block the formation of weak bonds between non-complementary strands and to guarantee the proper pairing of complementary molecules.

Given these findings and the intrinsic features of DNA molecules, it became evident that a specific DNA fragment could be identified from a biological sample by letting it hybridize, following denaturation, to a radiolabelled complementary molecule. An RNA strand, for example, could be used as a probe to gain insight into gene structure and function. The hybridization could even occur when the DNA was trapped onto a nitrocellulose membrane.

At that time, DNA fragments could be obtained by digestion with the recently discovered restriction enzymes (see Milestone 4) and by separation through electrophoresis in agarose gel (see Milestone 1). However, DNA recovery from the gel inevitably led to loss of material and a notable decrease in the resolving power of electrophoresis.

Southern had a genial intuition that he could transfer the DNA fragments directly from the gel onto a nitrocellulose membrane laid on top of it. The agarose gel being permeable, he could force liquid to pass through the gel by piling up, on top of the nitrocellulose, a stack of dry filter paper. Drawn by the flowing liquid, the DNA fragments could be soaked out of the gel. Following hybridization with radiolabelled RNA, autoradiography of the membrane revealed the specific fragments containing the sequence of interest, which appeared as sharp bands in the same position as they had been on the gel. It was finally possible to detect a specific DNA sequence from a smear, without having to purify it away from the rest of the genome.

Southern used his method to study bacterial and eukaryotic ribosomal genes, but its practice soon became widespread. It facilitated the study of gene structures and, only a few years later, the discovery of genetic defects (such as the loss of a restriction enzyme site underling sickle cell anaemia). Nowadays, the applications of the Southern blot span from basic to biomedical research, and from genetic engineering to forensics, yet the protocol remains surprisingly similar to that described by Southern over 30 years ago.

The method also inspired others to adopt a similar strategy for the study of different molecules. To emphasize the similarity with the Southern blot, the transfer of RNA and protein from a gel to a solid support were named northern and western blot, respectively.

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Nature Reviews Cancer and Nature Reviews Genetics

ORIGINAL RESEARCH PAPERS Marmur, J. & Doty, P. Thermal renaturation of deoxyribonucleic acids. *J. Mol. Biol.* **3**, 585–594 (1961) | Southern, E. M. Detection of specific sequences among DNA fragments separated by gel electrophoresis. *J. Mol. Biol.* **98**, 503–517 (1975)