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Not just “a clever way to detect whether DNA really made RNA”¹: The invention of DNA–RNA hybridization and its outcome



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ABSTRACT

The invention of DNA–RNA hybridization in 1960 by Ben Hall and Sol Spiegelman had a powerful impact on the theory and discourse of molecular biology. Yet, despite its importance, the story of this invention has barely been told. Hybridization allowed biologists to bridge the theoretical realm and the material world of organisms, to correlate a hypothetical concept of biological information transfer with a mechanism capable of making an RNA copy of DNA. During the early 1960s, Spiegelman and coworkers employed hybridization to investigate the origin of RNAs found in cells. They operationally defined messenger RNA and elucidated several aspects of genome organization. For Spiegelman, this was the culmination of his longstanding interest in the mechanism of enzyme/protein synthesis; for Hall, it was the beginning of a successful career in genetics. Other scientists immediately recognized the power of the technique and introduced improvements. In 1965, Gillespie and Spiegelman combined several modifications and described a procedure for hybridization that became standard. Since the 1970s, it has become an essential tool in biology and in biotechnology, and a core component in molecular techniques such as DNA microarrays. Notwithstanding its current success, the inventors' names have disappeared from the literature. This curiosity is discussed.

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“The very construction of the concepts is intertwined with the practices which operationalize them, give them empirical reference, and make them function as tools for the production of knowledge.” (Timothy Lenoir, in Rheinberger, 1997, pp. 16–17).

1. Introduction

The role that DNA–RNA hybridization (henceforth hybridization²) played in the construction of the nascent field of molecular biology is captured in Timothy Lenoir's words written above. The notion of rewriting genomic information, inscribed in

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¹ Judson (1979, p. 440).

² For a discussion of the various terms used at the time to describe nucleic acid duplex formation, see Suárez (2001), note 23.

deoxyribonucleotide sequence as a ribonucleotide sequence, was ontologically reified by this technique. Invented in 1960, it was swiftly adopted and adapted by scientists using it to produce facts and ideas concerning molecular-genetic processes and genome structure. For example, Suárez (2001) elaborates how during the 1960s, Roy J. Britten and his colleagues at the Biophysics Section of the Carnegie Institution of Washington adapted the technique to fit their investigative interests. I will return to this topic later. Since the mid-1970s, hybridization has become a core component of many DNA technologies that have revolutionized the study of biology. For example, it is found in fluorescence *in situ* hybridization (FISH) that permits the detection, quantification and localization of genes and RNA. It is a component of Southern blot that is used for the detection and separation of a specific DNA sequence. We also find hybridization in DNA microarrays used for the simultaneous assaying of thousands of genes by exposing DNA fragments to RNA probes. DNA technologies are employed today by scientists in their ambitious attempts to build a comprehensive parts list of genes and functional elements (non-coding DNA sequences) in the human

genome (ENCODE Project Consortium and the Human Genome Project).³ But a new revolution in genetic engineering is now occurring. *Science* magazine has recently announced the “CRISPR Revolution.” CRISPR-Cas9 is an enzyme that uses an RNA duplex (guide RNA) to form base pairs with DNA target sequences. The enzyme can then introduce site-specific modifications in the genomes of cells and organisms (Doudna & Charpentier, 2014). Many scientists believe that a discussion of the use of CRISPR-Cas9 technology to manipulate the human genome is needed. Some scientists are even calling for a moratorium especially since rumors that Chinese scientists have edited human embryos’ genomes have been confirmed (Cyranoski & Reardon, 2015).⁴

Initially, hybridization provided a novel means to prove genetic information transfer. In Judson’s words, it was “a clever way to detect whether DNA really made RNA,” thus lending a completely new kind of support for the hypothesis of messenger RNA (Judson, 1979, p. 440). Evidently, the technique has since far surpassed the role attributed to it by Judson. Yet, despite its success, the names of its inventors are rarely noted in today’s scientific literature. The purpose of this paper is to recount the rationale and the circumstances of the invention of hybridization and to illuminate some of the significant facts it helped to produce. In addition, I will describe its embedding in molecular biology and biotechnology, as well as discussing the dissociation of its inventors’ names from the invention itself.

In 1957, Francis Crick (1958) suggested the “central dogma of molecular biology,” offering a two-step mechanism of information transfer: from DNA to RNA and from RNA to protein.⁵ Whereas several comprehensive historical accounts describing the cracking of the genetic code (translation) and the discovery of the parts and operations involved in protein construction exist,⁶ no historical account centered on the elucidation of the mechanism of the first step of information transfer (transcription) is available. Giacomoni (1993), a former student of Spiegelman, wrote a brief account of the invention focusing on its empirical aspects and development but barely touching on its epistemological and discursive outcomes. Suárez (2001) describes the physical and chemical basis of hybridization that originated with Julius Mamur and Paul Doty’s work at the Conant Laboratory at Harvard University. In her account, hybridization is used to demonstrate the “close relationship existing between the construction of a phenomena and the development of experimental techniques in molecular biology.” (p. 35). For that purpose, a detailed and technical account of modifications made to the original procedure is given. Yet, the impact of the invention on the establishment of basic concepts and facts of the young field of molecular biology is not considered. Indeed, this important invention, as well as the contribution of biologists investigating transcription towards the elucidation of the mechanism of genetic information transfer is hardly discussed by historians (Judson, 1979, p. 440; Kay, 2000, pp. 230–231; Morange, 1998, p. 148).

In this paper, I follow Sol Spiegelman’s (1914–1983) endeavors to elucidate the mechanism of protein synthesis, focusing on the last part of his investigation, in which hybridization figured prominently. His inquiry into the mechanism of information transfer was the culmination of his longstanding interest in “biological specific synthesis,” that is, protein synthesis. His experimental systems consisted of yeast, bacteria, and bacterial viruses (phage), as well as a wide variety of techniques and tools that were introduced into biological research from the 1930s onwards. His studies exhibit a move towards an experimental and epistemological “molecular vision of life,” a path which was taken by many biologists during the first part of the twentieth century (Kay, 1996). Spiegelman’s molecular vision reflected a growing involvement of genes in protein synthesis, beginning with nucleoproteins, then with an RNA template that presumably served as a mold to configure the amino-acid chain. Finally, the direct involvement of genes was established using “molecular hybridization”⁷ to detect an “informational” RNA molecule that is a DNA transcript. By following Spiegelman’s research program, I will portray one of the paths that biologists took on their way to clarifying the process of protein synthesis.

My account makes use of scientific articles and recollections published in various journals. It also incorporates material obtained from the Sol Spiegelman Papers collection located at the National Library of Medicine, Bethesda.⁸ Also, in order to examine the dissociation of inventor’s names from the invention, I conducted a citation study of Gillespie & Spiegelman’s (1965) paper and reviewed several classical biochemistry/molecular biology textbooks written during the 1960s. This paper contains seven sections. Section 1 is an introduction. In Section 2, I describe Spiegelman’s interest in biologically specific synthesis that was manifested in his experimental work on enzyme adaptation (renamed “induction” in 1953⁹). I also present several models that attempted to explain the appearance of adaptive enzyme activity in cells cultured under certain growth conditions. In these models a conceptual link between genes and protein synthesis was eventually formed. Sections 3 and 4 are devoted to the introduction, around 1950, of the notion of “template” into biological thought, and to following its material and epistemological transformations. In Section 5, I elaborate on the rationale and the circumstances of the invention of DNA–RNA hybridization and the role that this technique played in giving an RNA template (eventually messenger RNA) operational meaning. In Section 6, the outcome of hybridization is described. Finally, in Section 7, the embedding of hybridization in the theory and practice of molecular biology as well as in biotechnology is discussed, as is the concomitant disappearing of the inventors’ names from the scientific literature.

2. Sol Spiegelman and “biologically specific synthesis”

During the first part of the 20th century, the notion of specificity played a significant role in biological thought and research concerning the action of hormones, as seen in the wide range of specific immunological response to a variety of antigens, and in respect

³ Nature milestones: DNA Technologies. <http://www.nature.com/milestones/mileDNA/index.html>.

Retrieved February 12, 2015. All About The Human Genome Project (HGP). <http://www.genome.gov/10001772>. Retrieved February 12, 2015; ENCODE: Encyclopedia of DNA Elements. <https://www.encodeproject.org/>. Retrieved February 18, 2015.

⁴ Nicholas Wade. (March 19, 2015). Scientists seek ban on method of editing the human genome. New York Times. <http://www.nytimes.com/2015/03/20/science/biologists-call-for-halt-to-gene-editing-technique-in-humans.html?emc=eta1&r=0>. Retrieved March 22, 2015.

⁵ The central dogma forbade information transfer from protein to RNA or DNA. Crick (1956), however, did acknowledge in a letter to Spiegelman the possibility of a genetic information flow from RNA to DNA.

⁶ Darden & Tabery (2010), Kay (2000), Morange (1998), Rheinberger (1997) and Judson (1979).

⁷ Spiegelman (The Discovery and Development of RNA: DNA Molecular Hybridization, n.d. [SSP, box 1 folder 1]).

⁸ Spiegelman, Sol. Sol Spiegelman Papers. 1929–1983. Located in: Modern Manuscripts Collection, History of Medicine Division, National Library of Medicine, Bethesda, MD; MS C 561. The library has scanned many documents and these can be found on the library’s website: Profiles in Science. Spiegelman’s at <http://profiles.nlm.nih.gov/PX/>.

⁹ Spiegelman, Monod, Pollock and Stanier were concerned about the evolutionary connotation of the term “adaptive,” as were other biologists, hence the renaming. See Cohen, Monod, Pollock, Spiegelman, & Stanier (1953).

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