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Review

Almroth Wright, opsonins, innate immunity and the lectin pathway of complement activation: a historical perspective

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Abstract

Two clinical tests − the erythrocyte sedimentation rate and the opsonic index − have long been known to non-specifically detect pathology based on their responsiveness to changes in serum proteins. In infections serum levels of specific antibodies increase. However, for healthy subjects Wright held that antibodies contributed minimally to opsonic activity (the complement-enhanced phagocytosis of microorganisms). The activity was present in newborn serum, was increased in the acute phase of an immune response prior to antibody increase, and was less specific. Furthermore, defective opsonization was associated with undue susceptibility to certain infections, for which a genetic basis was later found. With the demonstrations of complement-mediated lysis both of normal cells by foreign (plant) lectins, and of foreign cells (microorganisms) by animal lectins, it now appears that endogenous lectins correspond to the heat-stable component of Wright's serum opsonic activity. His work leads to the lectin pathway of complement activation with specificities limited to the recognition of relatively immutable surface sugars − predictable pathogen characters that contrast with the less predictable targets of the adaptive immune system.

Keywords: Acute phase response; Aggregation; Erythrocyte sedimentation rate; Immunodeficiency disease; Mannose-binding lectin; Predictable pathogen characters

1. Introduction

In his opening address to the third Cold Spring Harbor Symposium on immunology in 1989, Charles Janeway − calling for "a rediscovery of microbiology by immunologists" − argued that "the immune system has evolved specifically to recognize and respond to infectious microorganisms, and that this involves recognition not only of specific antigenic determinants, but also certain characteristics or patterns common on infectious agents" [1]. Almroth Wright would almost certainly have agreed. He dedicated his collected works − "Studies on immunisation and their application to the diagnosis and treatment of bacterial infections" − to Elie Metchnikoff and Paul Ehrlich [2]. It was "an endeavour to win from the intellectual seed sown by them a harvest for medicine." Wright wanted to employ immunization not only prophylactically to prevent subsequent infection, but also therapeutically to treat ongoing infections. Despite the immunogenic effect of such infections ("autoinoculations"), he supposed that the patients' immune defenses, especially in patients with localized infections, might not have been fully alerted; but by using the "opsonic index" this could be monitored. His work as pathologist at St. Mary's Hospital in London anticipated much of Janeway's address, but the medical applications were ridiculed in a 1906 play − *The Doctor's Dilemma* − by his friend, George Bernard Shaw [3]. I here describe how, despite decades of controversy [4−6], some fruits of Wright's hoped for harvest have now emerged.

2. The antibody pathway of complement activation

Metchnikoff in France had described the ability of certain cells (phagocytes) to ingest foreign organisms [7]. Ehrlich in

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Germany had described two soluble factors in body fluids (e.g. blood plasma) that could sequentially cooperate to destroy foreign microorganisms [8]. First there were the heat-stable antibodies ("Antikorper"), which were sometimes present in unimmunized animals ("Zwischenkorper;" natural antibodies), but were greatly increased in concentration in immunized animals. These combined specifically with the immunizing agent, so marking it as foreign (not-self). The second factor – the heat-labile "complement" that maintained a relatively constant concentration – would then bind and lyse the cell. At that time, antibodies – often referred to as "immune bodies" or "amboceptors" – were uncharacterized at the molecular level. They were named operationally after the various modes in which they were manifest – e.g. "agglutinins" when the plasma containing them caused individual bacteria to clump together (aggregate), and "lysins" when the bacteria were destroyed.

Citing Jenner and smallpox vaccination, Ehrlich had focused on prophylactic immunization, where prior intentional exposure to a less virulent (attenuated or killed) form of a microorganism would protect the recipient against a subsequent encounter with the corresponding virulent form. Politely putting aside for the time being "the very able investigations of Metchnikoff" on the complexities of phagocytosis that "were, to many investigators, inconclusive," Ehrlich chose to use tubes of washed red blood cells as his "research animal."

When red blood cells (corpuscles, erythrocytes) of one species were injected into an animal of another species, highly specific antibodies would appear in the latter's plasma. If this was heated to remove complement, then the antibodies could be measured by their abilities to agglutinate the foreign red cells ("hemagglutinins"). Antibodies could also be quantitated by measuring the hemoglobin that was released into the medium when complement was added ("hemolysins"). From experiments with such simple systems, Ehrlich was led to propose a scheme of molecular interactions that corresponds well with our present understanding. In his words, hemolysis requires "two components – the stable, which may be designated 'immune body,' and the unstable, which may be designated 'complement' – which acting together effect the solution of the red blood corpuscles."

This "classical pathway" of complement activation is now well characterized at the molecular level. The first component, C1q, interacts with an antibody when it has reacted with the surface of a red cell (when this is the antigen injected to elicit the antibody). There follows a cascade of sequential reactions – C1r and C1s, C2 and C4, C3, and then assembly of a five-member membrane attack complex (C5–C9). However, in 1989 Janeway implicated a non-classical, more primitive, complement pathway, which differed in some of the earlier-acting components [1].

3. Phagocytes need buttered bacteria

Wright and his colleagues at St. Mary's Hospital (Fig. 1) took Ehrlich's work to a higher technical level. They focused on the phagocytosis-enhancing properties of the plasma from *unimmunized* human donors. Rather than foreign red cells they took live bacteria. Rather than measure their lysis, the number of bacteria ingested by phagocytic cells (white blood cells; leukocytes) in a blood sample was recorded. Prior to the experiment, the blood sample could be spun in a centrifuge to separate the plasma from cells. These could then be treated separately (e.g. heated at 60 °C for 15 min) and reunited in various proportions, and in varying sequences, before or after incubating with the bacteria at 37 °C for 15 min – a time sufficient for ingestion but not for digestion.

It might be thought that plasma or serum (plasma less clotting factors) would merely provide a convenient physiological medium where, away from the living body, a phagocyte could continue its normal function. However, in 1903 Wright and Douglas reported that the main role of these fluids in their 37 °C incubation mixes was to prepare the bacteria for phagocytes to ingest [9]. In their words, "the blood fluids modify the bacteria in a manner which renders them a ready prey to the phagocytes." Thus, "we may speak of this as an '*opsonic*' effect (opsono – *I cater for; I prepare victuals for*), and we may employ the term 'opsonins' to designate the elements in the blood fluids which produce this effect." Likewise, the protagonist in *The Doctor's Dilemma* declared [3]: "Opsonin is what you butter the disease germs with to make your white blood corpuscles eat them."

With some bacteria (e.g. *Bacillus typhosus*), Wright and Douglas observed that a direct lytic effect of normal serum was the usual result, so that the opsonic effect was less apparent: "It is manifest that where disintegrative changes … are occurring under the influence of the serum, opsonic effects will be more or less thrust into the background" [10]. With others (e.g. *Staphylococcus aureus*), direct lysis was absent and opsonic effects were readily demonstrable [11]. Wright concluded [12]:

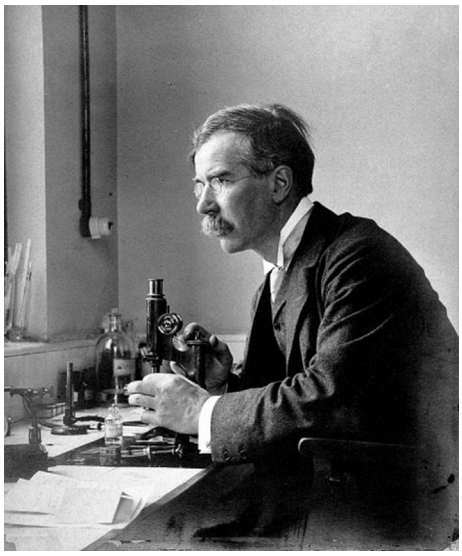

Fig. 1. Almroth Wright in his laboratory, circa 1900. Wellcome Images Library, London.

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