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EDITORIAL

Lectins: A brief review
Lectinas: Una revisión breve

The ability of plant agglutinins to distinguish between erythrocytes of different blood types led Boyd and Shapleigh (1954) to propose for them the name lectins, from the Latin "legere", to pick out or choose [1]. This term was later generalized to embrace all sugar-specific agglutinins of non-immune origin, irrespective of source and blood type specificity [2]. It was toward the end of the 19th century that evidence first started to accumulate for the presence in nature of proteins possessing the ability to agglutinate erythrocytes. Such proteins were referred to as hemagglutinins, or phytoagglutinins, because they were originally found in extracts of plants. It is generally believed that the earliest description of such a hemagglutinin was by Peter Hermann Stillmark in 1888. This hemagglutinin, which was also highly toxic, was isolated from seeds of the castor tree (*Ricinus communis*) and was named ricin. Subsequently, H. Hellin demonstrated the presence of another toxic hemagglutinin, abrin, in extracts of the jequirity bean (*Abrus precatorius*). Well known for being the first to crystallize the enzyme urease, for which he was later awarded the Nobel Prize, James B. Sumner in 1919 isolated from jack bean (*Canavalia ensiformis*) a crystalline protein that he named concanavalin A, unknowingly obtaining a pure hemagglutinin for the first time. Nearly two decades passed before Sumner and Howell (1936) reported that concanavalin A agglutinates cells such as erythrocytes and yeasts and also precipitates glycogen from solution. They further showed that hemagglutination by concanavalin A was inhibited by sucrose, demonstrating for the first time the sugar specificity of lectins [3].

Already the early results obtained by Stillmark indicated some selectivity in the ricin-induced agglutination of red cells from different animals. This observation was corroborated and further extended by Karl Landsteiner from the University of Vienna, the discoverer in 1900 of the human A, B, and O blood groups. The 1940s saw the discovery, made independently by William C. Boyd and by Karl O. Renkonen, of the human blood type specificity of the hemagglutinins. They found that crude extracts of the lima bean, *Phaseolus limensis*, and the tufted vetch, *Vicia cracca*, agglutinated blood type A erythrocytes but not blood type B or O cells, whereas an extract of the asparagus pea, *Lotus tetragonolobus*, specifically agglutinated blood type O erythrocytes. Since then, additional hemagglutinins specific for blood types A and O (but not B) have been discovered, as well as several for other blood types, such as N (*Vicia graminea lectin*), T (peanut agglutinin, PNA) and Tn (the lectins of *Vicia villosa* and *Moluccella laevis*). The basis of these different binding specificities is now known to be due to genetically determined erythrocyte surface expression of distinct complex carbohydrates.

Two major discoveries made in the early 1960s were instrumental in bringing lectins into a limelight beyond hemagglutination. The first of these was by Peter C. Nowell (1960) who found that the lectin of the red kidney bean (*Phaseolus vulgaris*), known as phytohemagglutinin (PHA), is mitogenic, that is, it possesses the ability to stimulate lymphocytes to undergo mitosis [4]. This discovery had a revolutionary impact on immunology in that it shattered the view, held until then, that lymphocytes are dead-end cells incapable of dividing or differentiating further. A most valuable outcome of such studies was the discovery in the 1970s by Robert C. Gallo of T cell growth factor, now known as interleukin-2, in conditioned medium of normal human lymphocytes stimulated by PHA [5]. Joseph C. Aub made the second major discovery [6, 7], finding that wheat germ agglutinin (WGA) has the ability to preferentially agglutinate malignant cells.

Numerous lectins thus become available over time and interest in them was greatly stimulated by the demonstration that they are invaluable tools for the detection, isolation, and characterization

of glycoconjugates, primarily of glycoproteins, for histochemistry of cells and tissues and for the examination of changes that occur on cell surfaces during physiological and pathological processes, from cell differentiation to cancer. The occurrence of hemagglutinins derived from animals was noted quite early, almost all from invertebrates or lower vertebrates, but until the middle of the 1970s, only the three of these (of eel, snail, and horseshoe crab) were isolated and characterized. The first of the animal lectins shown to be specific for a sugar (L-fucose) was from the eel [8]. The isolation in 1974 of the first mammalian lectin, the galactose-specific hepatic asialoglycoprotein receptor, was an outcome of the investigation by Gilbert Ashwell and Anatol G. Morell of the mechanisms that control the lifetime of glycoproteins in blood circulation [9, 10]. Since the beginning of the 1980s, the number of purified animal lectins has expanded, largely thanks to the advent of recombinant cloning techniques.

During the past few years, the number of lectin primary and 3D structures has increase dramatically, with some 200 of the latter having been elucidated (www.cermav.cnrs.fr/lectines). In addition, many structures of lectin–carbohydrate complexes have been solved. Based on an analysis of the then known amino acid sequences of animal lectins, Kurt Drickamer proposed in 1988 that the carbohydrate-binding activity of most of them resides in a limited polypeptide segment, designated by him as the carbohydrate-recognition domain (CRD) [11]. He named the CRD found in the galectins S-CRD and that found in the C-type lectins C-type CRD. Currently several types of CRD have been discerned in addition to those just mentioned, each of which shares a pattern of invariant and highly conserved amino acid residues at a characteristic spacing. On this basis it was possible to divide the majority of the animal lectins into structurally related families and superfamilies, with the C-type lectins (CTLs) being the most widely occurring. The majority of the CTLs are large, asymmetric transmembrane glycoproteins, in which the CRD is attached to a variable number of structurally and functionally different polypeptide domains. In contrast, the galectins are generally small, soluble, non-glycosylated proteins and, unlike the CTLs, do not require structural stabilization via Ca^{2+} complexing for their activity. Members of the CTL superfamily are grouped into three families: selectins, collectins, and endocytic lectins.

Myeloid cells are key players of physiological responses to pathogen invasion or tissue damage. Members of the C-type lectin receptor (CLR) family stand out among the specialized receptors utilized by myeloid cells to organize these responses. CLR ligands include carbohydrate, protein, and lipid components of both pathogens and self, which alternately can induce endocytic, phagocytic, antimicrobial, pro-inflammatory, or anti-inflammatory responses, which are either protective or not during an infection [12, 13]. These varied outcomes rely on a resourceful structure/repertoire of tools for CLR signaling that includes tyrosine-based motifs that recruit kinases, phosphatases, or endocytic adaptors as well as non-tyrosine-based signals that modulate the activation of other pathways or couple to the uptake machinery. Some myeloid C-type lectin receptors (CLRs) detect the molecular signatures of microbes, fungal pathogens, but as yet little is know about the role of these receptors in bacteria, viral and parasitic interactions. Whereas other myeloid CLRs recognize damaged cells, oxidized lipids, and other self-alterations indicative of abnormality. Myeloid cells express many members of the galectin and Siglec families of lectins. C type lectins in myeloid cells include, in group II, DC-SIGN (In human, no murine homolog), SIGNR1 (In mouse, no human homolog), macrophage C -type lectin (MCL), langerin, macrophage galactose –binding (MGL) and it's isoform Dendritic Cell – Asialoglycoprotein receptor (DC-ASGPR); in group V, Dectin -1 and MDL-1 and in group VI macrophage mannose receptor (MMR) and DEC-205 [12, 13]. Future studies will no doubt shed light on the specific roles in host defenses, cell-cell communications, tissue regeneration, and other key functions of this diverse and fascinating family of proteins.

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