

EDITORIAL

Cell sweeteners: the role of carbohydrates in cell interactions

The Th2 cytokine response has long been associated with allergic disease, and as IL-4 heightens the Th2 response thus exacerbating the situation, positive identification of the cells producing IL-4 is important. This could open the way for development of therapeutic treatments to modify or block IL-4 production, thus attenuating the Th2 response. While T cells and mast cells are obvious candidate sources for IL-4, basophils have also been associated with this cytokine. In this issue, Hoffman et al. [1] have shown that lectins can stimulate IL-4, not only in basophils but also in mast cells and eosinophils. These are interesting observations with implications for our understanding of the Th2 response.

Lectins are naturally occurring carbohydrate-binding proteins (commonly glycoproteins) of non-immune origin and are found in plants, fungi, invertebrates and vertebrates, including man – indeed, it is probable that they occur in all living species. Individual lectins bind to carbohydrate residues in a highly specific manner and by so doing can alter the cellular response. It is not clear by what mechanism the lectins are causing the stimulation of IL4 production in Hoffman's studies, but as these are living cells, the lectins are presumably binding to carbohydrates on the surfaces of the cells. The binding of the multivalent lectins to cell surface carbohydrates could have several different effects. Binding to a specific carbohydrate may be sufficient to mediate a signal stimulating IL-4 secretion directly. Alternatively, lectins may cross-link proteins via carbohydrate residues, reducing the mobility of the proteins within the cell membrane or agglutinating cells altering normal cell-to-cell interactions; either of these could result in altered IL-4 production. Lectins are widespread in our diet and are generally resistant to digestion, which opens up the possibility of pathophysiological interactions with cells of the immune system. In rats, long-term feeding of low doses of some commonly occurring lectins resulted in an increase in pancreatic growth [2]. Other studies on rats fed a diet containing the lectin from wheat germ compared to a diet deprived of this lectin demonstrated that the deprivation resulted in suppression of lymphocyte activity from primary and secondary lymphoid organs [3]. These results show the potential for dietary lectins to influence cellular responses, including inflammatory responses, via carbohydrate interactions and are consistent with the results obtained by Hoffman et al. [1].

It is becoming clear that carbohydrates have a much broader role in cellular interactions than has previously been recognized. In recent years, carbohydrates have become a focus of attention as better techniques for understanding their interactions have become available. Cellular carbohydrate expression changes depending on the environment and such changes in carbohydrate expression are now associated with a number of disease states. Much work has been done in the

field of bacterial and viral attachment to host cells, probably the best known example being the influenza virus that has a surface haemagglutinin that binds to sialic acid containing glycans on cell surfaces in the upper respiratory tract mucosa. This enables the virus to colonize the mucosa and for fusion of the virus to take place resulting in infection [4, 5]. Another bacterium that causes persistent problems is *Pseudomonas aeruginosa*. This is a very virulent bacterium that colonizes compromised airways. It is known to produce two lectins, and both these lectins inhibit ciliary function and are probably involved in the attachment of the bacteria to the epithelial cells in the respiratory tract, thereby facilitating colonization [6]. This bacterium is notoriously difficult to treat with conventional antibiotics in immuno-compromised patients. However, there is a case report describing an infant who had received chemotherapeutic treatment for a neuroblastoma and who subsequently developed a *P. aeruginosa* infection. This infection did not respond to conventional antibiotic treatment and so a series of galactose/fucose inhalations (these are the carbohydrates for which these lectins are specific) were applied. This resulted in elimination of the bacteria [7] as shown by microbiological testing and recovery of the patient. This is probably the first time that a lectin-based therapeutic principle has been applied to *P. aeruginosa* infections and with a successful outcome. Generally, drug companies tend to develop complex biochemical therapeutic treatments that are extremely expensive and have a high drop-out rate due to toxicity or other problems. Such simple therapies as sugar aerosols do not seem to have attracted their attention, possibly because basic sugars are not patentable.

The cancer field is also an excellent example where the study of carbohydrate expression has yielded results that pertain to the prognosis of the patient. Determination of carbohydrate profiles, in particular of primary tumours, can now determine the metastatic potential of the tumour and hence affect the outcome of the disease demonstrating the importance of altered carbohydrate expression. For example, the ability of lung adenocarcinomas to metastasize has been linked to the expression of a particular form of galactose on the cells [8]. The presence of *N*-acetylgalactosamine residues on cancer cells including breast, stomach and colorectum amongst others can be associated with metastasis and poor prognosis [9]. Clearly, the knowledge that certain tumours are more likely to metastasize will assist in developing the most appropriate treatment regimens.

In many cases, these studies have been undertaken using lectin analysis of the cell surface carbohydrate structure. By using combinations of lectins, it is possible to formulate a carbohydrate profile for both normal and diseased states and thus identify any altered expression associated with the

disease. Lectins can be divided into broad categories of specificities, and from this broad ordering a more precise classification of each lectin can be achieved. Some lectins will only recognize their specific carbohydrate in a particular conformation – the α 1,2 fucose-specific lectin *Ulex europaeus* I does not recognize fucose with an α 1,6 linkage as steric hindrance prevents accessibility. This means that some lectins are highly specific even to the conformational structure of the carbohydrate and make powerful recognition tools.

In addition to the use of lectins as tools for determining carbohydrate expression, the functionalities of naturally occurring lectins in the human are gradually being determined. A number of different lectins have now been identified, some of the most notable being selectins. Selectins are a family of transmembrane proteins that bind to cell surface carbohydrate residues. This binding results in the adhesion of leucocytes to endothelial cells and to other leucocytes as a response to tissue damage. The selectin–ligand interactions occur rapidly to allow tethering and then dissociate rapidly to allow the cell to roll along the endothelium in a controlled manner. This allows the process of extravasation into the underlying tissues to take place [10]. The presence of selectins is normally tightly controlled; however, in certain diseases excess selectins are expressed and an abnormal accumulation of leucocytes can occur, which contributes to the pathogenesis of the disease. An example of this is rheumatoid arthritis where increased fucosylation has been detected [11, 12] and accumulations of inflammatory cells detected. Up-regulation of selectins has also been detected following atherothrombotic strokes resulting in acute inflammation, which contributes to brain damage [13]. Another group of lectins worthy of note are the galectins. Galectins bind specifically to galactose and are found not only in vertebrates but also in invertebrates and fungi. Several biological processes are implicated as being galectin targeted in mammals such as development, morphogenesis, tumour metastasis and apoptosis. Galectin-1 is found in many organs, for example, muscle, peripheral nerves, brain and thymus. In 1999, Pace et al. [14] demonstrated that galectin-1 induced apoptosis in cultured human thymocytes. They were also able to show that the induction of apoptosis was linked to a spatial re-organization of some of the cell surface receptor molecules, namely CD45, CD43 and CD7 [14]. These molecules moved from a uniform distribution to highly localized, separate patches on the cell surfaces. This is a good example of the importance of lectins to basic biological systems and the significance of lectin–carbohydrate interactions.

In summary, IL-4 production has been shown to be induced by a number of factors, but the actual mechanisms behind this induction are not clearly understood. With the use of lectins, Hoffman et al. have indicated that the increased production of IL-4 by basophils may well be carbohydrate mediated. This is a significant result and is a good example of the importance of carbohydrates in cellular processes, providing further clues to developing therapeutic treatments.

References

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