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Letters to the editor

MHC class II molecules and the immune response to the ABBOS peptide of bovine serum albumin: prelude to Type 1 (insulin-dependent) diabetes?

Dear Sir,

The recent for debate paper by Robinson et al. [1] raises a number of issues concerning the putative mechanisms by which certain MHC molecules of the class II region (DR and DQ) contribute to the pathogenesis of, or confer protection from, Type 1 (insulin-dependent) diabetes. While speculation about immune mechanisms can range far afield with no quick experimental verification, the area of peptide binding to particular class II molecules is one where we can gain some insight from the recent literature on the matter.

Since no three-dimensional structure of a class II MHC molecule has been reported to date, we must limit ourselves to the recent excellent studies on the crystal structures of mouse and human MHC class I molecules complexed with various antigenic peptides [2–5]. The lessons that emerge from these studies can be summarised as: 1.) the three-dimensional structures of the polypeptide backbones of different human and mouse MHC class I molecules are nearly identical giving the major theme of the β-pleated sheet floor and the two α-helical walls forming an antigenic groove. 2.) Binding of the antigenic peptide to the class I molecule is via one or two and at most three anchor residues. Each specific class I molecules has its own anchor specificities at different positions of the antigenic peptide. The anchor specificities arise from the particular architecture of the antigenic groove, contributed by amino acid residues from the floor as well as from the walls of the groove. There is considerable latitude as to the type of amino acid that can fit into the remaining positions of the antigenic peptide. 3.) The forces that hold the antigenic peptide inside the groove are mostly hydrogen bonds between the peptide bond $\overset{N}{\underset{H}{}} - C = O$ groups of the antigenic peptide and the various amino acid side groups from the class I molecule.

It should be noted that the extensive biochemical research conducted up to now on the subject has shown that class I MHC molecules bind mostly antigenic peptides with 8–10 amino acids [2–5]. On the other hand the antigenic peptides that bind to class II molecules (in mouse and man) may range from 13 to 25 residues [6, 7]. The structural basis for this is unknown but it may have to do with the ends of the two helices of the class II molecule. It is obvious from complexes of class I molecules and antigenic peptides (8–10 amino acids in length) that any considerably longer peptide would have to bulge out of the groove [2–5], thus preventing simultaneous identification of peptide plus MHC molecule by the T-cell receptor. The model of the MHC class II molecule based on the class I structure did not assign a precise secondary structure at three of the four ends of the opposite α-helices [8]. Perhaps, there is more flexibility at these ends, accounting for the longer peptides allowed by class II molecules. At one end of the putative antigen binding groove of class II lies Arg 76, an invariant residue in all class II molecules known to date, and opposite to it the celebrated β57 residue (mostly Asp in protective class II molecules). At the other end, albeit at a more imprecise position, lies residue 52 (Arg in "susceptible" molecules). It seems that the possible interactions between 76Arg, β57Asp and one end of the putative diabetic autopeptide cannot be ignored.

Since there is ample evidence that class II molecules also have certain "anchor" residues [6, 7], we must also assume that the mode of interaction between the antigenic peptide and the MHC molecule must in many respects resemble the counterpart of class I [8]. The model proposed by Robinson et al. [1] runs foul of this rule since it considers only interactions between the ABBOS peptide and the α-helix of the DQβ or DRβ chain and not at all the DQ or DR β-chain, or any residues from the β-pleated sheet floor. Furthermore, unless we assume that both the third hypervariable region of DQβ or DRβ and the ABBOS peptide are in an extended conformation (an assumption with no supportive evidence in the case of the class II molecule) the interactions that the authors list between these two structures cannot occur, as many of the DQβ-chain residues in this region would point away from the antigen binding groove [8].

Three other points used by the authors in their proposed mechanism deserve mention: 1.) it is not necessary for the beta cell to express class II molecules for an autoimmune attack to begin. It has been shown that transgenic mice carrying a gene for a viral protein in their beta cells and expressing the relevant T-cell receptor in their repertoire are tolerant to the protein, yet become diabetic upon infection with the same virus [9]. 2.) The density of expression of the various class II molecules on the surface of antigen presenting cells is another unknown; it has been presumed to be identical for all molecules, but it seems that different regulatory elements exist within the various genes [10]. 3.) That the antibodies against bovine serum albumin recognise the ABBOS peptide does not necessarily mean that this peptide is the restriction element for class II binding. Thus, another peptide from bovine serum albumin might be a better candidate to test the author's hypothesis, after taking into account the structural restrictions outlined above.

Yours sincerely
G. K. Papadopoulos

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Note added in proof. The three-dimensional structure of the HLA-DR1 molecule has recently been reported (Brown et al. (1993) Nature 364: 33–39) and shows many similarities to published MHC class I structures. The three principles of peptide binding outlined above seem to hold. Likewise, the ends of the two α-helices are closer to the β-sheet floor, permitting longer peptides to bind and allowing for the formation of a salt bridge between α76Arg and β57Asp, directly under the bound peptide.

Response from the author

Dear Sir,
In reply to Dr. Papadopoulos, I would agree with him that we can only make guesses about the manner in which class II HLA antigens and the peptides they bind interact. As he points out, the evidence favours a model in which class II antigens may bind much longer peptides than do class I antigens. The anchoring is presumed to be by aminoacid residues that hydrogen bond to various parts of the HLA class II structure. In our model we chose charged residues belonging to the third hypervariable region of DR or DQ-β molecules as likely discriminators which might either assist or repel binding of a peptide such as ABBOS by hydrogen bonding or by charge repulsion or attraction. The actual binding may or may not be mediated through these "discriminator" residues, but in our hypothesis they strongly influence the binding function.

Teleologically such discriminators must exist otherwise specificity and selection of peptide binding by class II alleles would not be a reality. As Dr. Papadopoulos remarks, "the alignment of the ABBOS peptide in the antigen binding groove must be performed again" when we know more about anchor specificities of class II molecules.

We all look forward to the day when this is possible.

Yours sincerely,

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Evolution of the glucokinase glucose sensor paradigm for pancreatic beta cells

Dear Sir,
In a recent review [1] Dr. P. J. Randle makes the claim of having discovered glucokinase in the pancreatic islet [2] and relegates to the confirmatory category our report which demonstrated directly, and for the first time, the presence of this enzyme in pancreatic islet tissue [3]. Dr. Randle's account distorts historical facts. A correction is in order.

Studies of Grodsky and collaborators [4] and of Coore and Randle [2] were the first to surmise in the early 1960s, that islet beta cells might be freely permeable to hexoses including D-glucose and that sugars, which are suitable substrates for hexokinases and thus glycolysis, are capable of eliciting insulin release. They suggested a link between stimulant fuel catabolism and hormone releasing function in beta cells. However, the approach taken by these investigators was incapable of distinguishing which of the four known glucose phosphorylating enzymes might be involved, because their studies were indirect and because the inhibitors of hexokinases (D-mannoheptulose and 2-desoxyglucose) lacked specificity or were ineffective at the concentrations they applied. Attempts by Ashcroft and Randle from 1968 [5, 6] to resolve this issue by direct analysis of glucose phosphorylation in homogenates of isolated islets, seemed to show the presence of low K_m hexokinase activity but a lack of glucokinase. Our first publication on this topic appeared in May 1968 [3], and demonstrated that islet tissue contained both (a) low K_m hexokinase(s) and a high K_m hexokinase (which we classified as glucokinase). This paper also reported the presence of glucose 6-phosphatase, confirming the data of Taljedal [7]. Additionally it provided the first clear direct evidence that intra- and extracellular glucose of islet cells equalized within minutes of an i. v. glucose load thus resembling liver cells. Glucose loading caused elevations of islet glucose 6-phosphate and fructose 1,6-bisphosphate presumably a manifestation of activation of glycolysis.

On the basis of these data we were able to formulate a plausible concept of beta cell glucose metabolism involving glucokinase as a key element [3]:

"The scheme of carbohydrate metabolism of the islets of Langerhans, emerging from these and other studies, has great similarities to the situation found in liver. The membrane properties of β-cells, the probable presence of two glucose phosphorylating enzymes with high and low affinity for the substrate, and the ability to liberate free glucose from glucose 6-phosphate constitute ideal conditions for rapid adjustments of glycolysis to blood glucose levels."