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Review

The role of major histocompatibility complex molecules in luteal function

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Introduction

One of the amazing features of the corpus luteum (CL) is the rapidity with which a very heterogeneous population of cells becomes organized into a functional unit. These diverse cells then communicate both directly and through paracrine mediators to facilitate the steroidogenic function and also the transient nature of the CL. Once the hormonal regulators of luteal function and demise (for example, LH and prostaglandin $F_{2\alpha}$) had been clearly delineated, considerable effort in the late 1970s and 1980s was spent characterizing the morphological and functional characteristics of the large and small steroidogenic cells. This was followed in the 1990s by increased interest in the roles that nonsteroidogenic cells, including endothelial cells, fibroblasts, pericytes and immune cells, might have in luteal function. It is now thought that the nonsteroidogenic cells are very active participants in regulating the functional capacity and lifespan of the CL. These cells communicate with the steroidogenic cells through the paracrine signaling molecules that they produce, and also through direct cell contacts. One form of direct cell-cell signaling that may serve to activate resident immune cells is major histocompatibility complex (MHC) molecule-dependent interaction between luteal cells with T lymphocytes. Expression of MHC molecules, and recognition of antigenic peptides presented in the context of MHC molecules, serves as a means to regulate the activation of T lymphocytes, thus controlling cytokine production and/or cytolysis.

Expression of MHC Molecules by Luteal Cells

Like the majority of other somatic cell types, luteal cells express class I MHC molecules. What is surprising is that luteal cells of several species, including the cow, also express class II MHC molecules [1-5]. However, the identity of cells expressing class II MHC in the CL is somewhat in question. Class II MHC expression is typically limited to cells of the immune system that are regarded as "professional" antigen presenting cells, such as macrophages, dendritic cells, and to a lesser extent, B cells. Macrophages present within the CL would therefore certainly account for a percentage of the class II-positive cells. However, flow cytometric studies of dispersed bovine and ovine luteal cells demonstrated the presence of class II MHC molecules on both large and small cell populations [1,2], suggesting that, in addition to luteal macrophages (which would be included in the small cell fraction), the steroidogenic luteal cells also express class II MHC. Further, the bovine large luteal cell population was subdivided into two groups, large dense cells and large less-dense cells [1]. Both populations contain class II MHC-positive cells, but the large less-dense population contained the highest percentage of class II MHC-positive cells. The identity of the cells comprising these two populations is not known, but it is possible that one population represents the large steroidogenic cells, and the other population is composed of aggregates of luteal endothelial cells. A subpopulation of luteal endothelial cells expressing class II MHC has recently been identified [6].

In the human, luteinization induces the expression of class II MHC molecules on granulosal cells [7], and expression of both class I and class II MHC molecules increases on granulosal cells in the late luteal phase [3]. In contrast, minimal class II MHC expression is detected in developing bovine CL [1]. Class II MHC expression is

elevated in the bovine CL by midcycle, and in bovine and ovine CL, class II MHC expression is higher near the time of luteal regression compared with midcycle [1,2,5]. In contrast to the bovine and ovine CL, class II MHC expression in the equine CL is not elevated until after the decline in circulating progesterone concentrations associated with initiation of luteal regression [4]. Significantly, in each of these species, expression of class II MHC is substantially less in CL from pregnant animals compared with non-pregnant animals [1,2,4]. In the chicken, cells expressing class II MHC have been identified in the theca layer of normally growing and pre-ovulatory follicles [8,9]. The percentage of cells expressing class II MHC was greater in post-ovulatory follicles and atretic follicles compared with pre-ovulatory follicles, and class II MHC-positive cells are found in both the thecal and granulosal layers of post-ovulatory and atretic follicles [9].

Given the information available describing the expression pattern of class II MHC molecules in the CL, a role for class II MHC molecules in the process of luteal regression has been proposed. The increase in expression of class II MHC molecules between early and midcycle CL [1] coincides with the acquisition of luteolytic capacity. Expression of class II MHC molecules on the surface of luteal cells increases near the time of natural luteal regression and when luteal regression is induced by $PGF_{2\alpha}$ [1,5] but is lower in pregnant compared to non-pregnant animals [1,2,4]. From this observation it can be inferred that class II MHC expression must be attenuated as part of the mechanism that inhibits luteal regression during maternal recognition of pregnancy. In addition, bovine luteal cells stimulate T lymphocyte proliferation *in vitro*, and they are more potent stimulators of proliferation when derived from CL collected after administration of $PGF_{2\alpha}$ to the cow [10]. This indicates that there is a change in the character of luteal cells that enhances their ability to stimulate the activation of T lymphocytes.

A physiological role for MHC molecules in luteal function is supported by the observation that both class I and class II molecules are expressed by luteal cells *in vivo*, and the expression of class II molecules varies with functional state of the CL. These observations have given rise to the hypothesis that the demise of the corpus luteum may involve local autoimmune-response mechanisms facilitated by increased expression of cell surface class II MHC at the time of luteal regression.

Major Histocompatibility Complex Molecules, Antigen Processing, and Autoimmunity

Stimulation of T lymphocyte activation is dependent on the specific interaction of a T cell receptor for antigen (TCR) on the T cell with MHC molecules located on the surface of the target cell [11]. The outcome of binding of the TCR to the MHC molecule is determined by the peptides bound to the MHC molecules. In the context of T cell responsiveness to a given cell or tissue, changes in the array of MHC-bound peptides presented to T lymphocytes can determine whether T cells are activated by the MHC molecules in a given tissue, or alternatively, whether T cells will remain in an unactivated state, a condition known as immunological tolerance.

Antigenic peptides that are presented to T cells via MHC molecules are derived from proteins that are proteolytically digested into short peptides prior to binding to MHC molecules. Collectively, the proteolytic degradation of antigenic proteins and the binding of the resulting short peptides to MHC molecules is called antigen processing. Since antigen processing can determine the types of peptides bound to MHC molecules, this process can impact whether cells within a tissue are able to activate T lymphocytes, thereby stimulating an immune response.

Class I MHC

Processing of peptides for presentation in the context of class I MHC molecules is carried out by the proteasome. The proteasome is a cytosolic protease complex composed of multiple subunits that is responsible for the majority of intracellular protein turnover, and also generates peptides that are presented to T cells via class I MHC molecules (Figure 1; [12]). The catalytic core of the proteasome, referred to as the 20S proteasome, is composed of two heterologous families of subunits, termed α and β subunits. The proteasome β subunits contain the active proteolytic sites [13]. The composition of the 20S proteasome is balanced between expression of constitutive β subunits under normal conditions, and expression of IFN-γ-inducible subunits during inflammatory conditions. Interferon-γ induces the replacement of constitutively expressed β-subunits with alternative β-subunits involved in antigen processing [14-18]. The genes encoding two of these IFN-γ-induced subunits, LMP2 and LMP7, are located within the class II MHC gene region [19-21] and these subunits have limited homology to the constitutive subunits Y and X, respectively [14,22]. The third IFN-γ-inducible subunit, originally termed MECL-1 and also referred to as LMP10 [17], is similarly homologous to the constitutive β-subunit Z [23]. Thus, replacement of the constitutive β-subunits X, Y and Z with the IFN-γ-inducible subunits (LMP7, 2 and 10) alters the peptide cleavage patterns of the proteasome [24,25], resulting in alterations in the repertoire of antigenic peptides presented by class I MHC molecules. Interestingly, the IFN-γ-inducible subunits and their constitutive homologues seem to be reciprocally regulated. Tissues expressing high levels of LMP2, LMP7, or LMP10 were observed to have low levels of the constitutive homologous subunits [26]. Also, IFN-γ coordinately induces expression of LMP2, LMP7 and LMP10 with

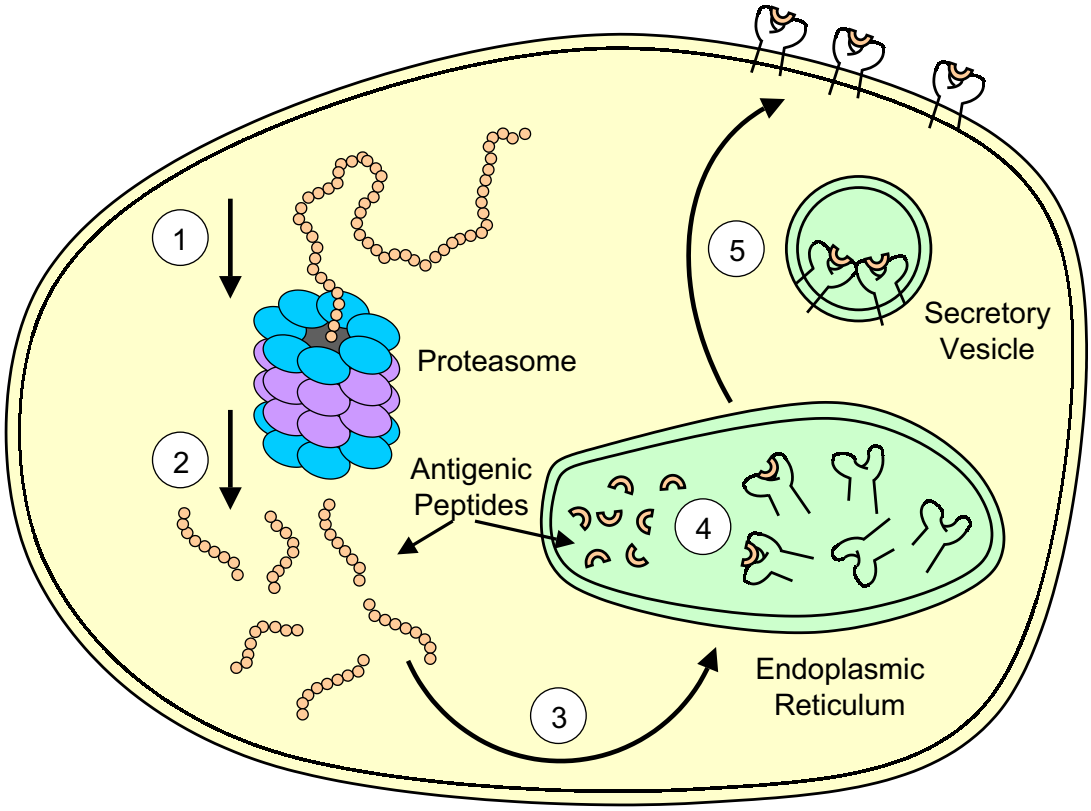

Figure 1
Schematic representation depicting processing of antigens presented by class I MHC molecules. 1) Intracellular proteins are proteolytically degraded within proteasomes. 2) Proteolytic degradation of intracellular proteins yields antigenic peptides of nine to eleven amino acids. 3) Antigenic peptides generated by the proteasomes are transported into the endoplasmic reticulum. 4) Newly synthesized class I MHC molecules bind antigenic peptides within in the endoplasmic reticulum. 5) Class I MHC-antigenic peptide complexes are exported through the Golgi and to the cell surface, for presentation of antigenic peptide to $CD8^+$ T cells.

concurrent reduction in expression of the constitutive homologues [17].

The most notable instance in which IFN-γ-inducible proteasome subunits are suspected to play a role in induction of an autoimmune response is autoimmune thyroiditis. The thyrocytes themselves appear to act as antigen presenting cells during the progression of the disease, stimulating the activation of T lymphocytes [27]. Studies of patients with Grave's disease and Hashimoto's thyroiditis, both of which are autoimmune thyroid disorders, found very high expression of LMP2 and LMP7 in the thyrocytes themselves [28]. This implies that proteasomes in these cells generate peptides that, when bound to class I MHC molecules, stimulate the activation of $CD8^+$ cytotoxic T lymphocytes, which infiltrate the thyroid tissue in massive numbers and exert cytotoxic effects on the thyrocytes [29].

We have recently demonstrated that interferon-γ-inducible subunits of the proteasome (mRNAs and protein) are expressed within the bovine corpus luteum [30]. Since bovine luteal cells isolated from regressing CL more potently stimulate T lymphocyte proliferation compared to luteal cells from midcycle CL [10], we hypothesized

that IFN-γ-inducible proteasome subunits would be upregulated in luteal tissue near the time of luteal regression. Such a change in proteasome subunit expression could induce alterations in the array of self-peptides presented to T cells in the context of class I MHC molecules during luteal regression, which could explain the enhancement in the ability of luteal cells to stimulate T cell activation following $PGF_{2\alpha}$ administration. However, we discovered that LMP7 and LMP10 were expressed in the CL at all stages of the estrous cycle, with no upregulation following induction of luteal regression with $PGF_{2\alpha}$. No changes were observed in LMP7 expression throughout the estrous cycle, but LMP10 expression was less in early CL, and greater in midcycle and late CL [30].

Class II MHC

Class II MHC molecules, typically expressed on antigen presenting cells of the immune system (ie. macrophages, dendritic cells and B lymphocytes), bind short peptides derived from intracellularly processed proteins [31]. Class II MHC molecules are heterodimeric proteins composed of non-covalently associated α and β chains. Assembly of the class II MHC complex occurs within the endoplasmic reticulum (ER), and involves not only α and β chains, but a third, non-polymorphic glycoprotein called the invariant chain (Ii). As class II MHC molecules are synthesized, they immediately bind to Ii, a portion of which occupies the peptide binding groove of the MHC molecule [32]. Invariant chain serves a dual function, directing intracellular transport of class II MHC molecules [33,34] and ensuring that binding of "inappropriate" peptides does not occur prematurely [32]. The MHC class II-Ii complex is then transported into endosomes, in which proteolysis by cathepsins and lysozomal proteases degrade the Ii into a peptide called class II-associated invariant chain peptide (CLIP; [35,36]). Prior to binding of antigenic peptides by class II MHC molecules, the CLIP fragment bound to the peptide binding groove must be removed. A class II MHC-like heterodimeric protein generically referred to as DM co-localizes with class II MHC molecules in endosomal compartments [37] and catalyzes the removal of CLIP from the peptide binding groove of the class II MHC molecule [38,39]. Following CLIP removal, the class II MHC molecule is free to bind processed antigen, before transport to the cell surface (Figure 2). The ability to process and present antigen in a manner dependent on class II MHC can be conferred to non-antigen presenting cells by transfection with a class II MHC molecule, Ii, and DM. These appear to be minimal yet sufficient components required for reconstitution of the antigen processing machinery [40].

Numerous autoimmune diseases are associated with aberrant expression of class II MHC molecules, including insulin-dependent diabetes mellitus and autoimmune thyroiditis, which are endocrine autoimmune disorders. In these diseases, the target cells express Ii and DM molecules, indicating that they are acting as antigen presenting cells capable of stimulating activation of $CD4^+$ T cells. Both Ii and DM mRNAs are expressed within bovine luteal tissue, with DMα and DMβ being elevated in midcycle compared to early CL [41], and bovine luteal cells are potent stimulators of class II-MHC dependent T cell proliferation [10]. Therefore, cells within the CL are able to process and present antigens to T cells in the context of class II MHC, which may predispose luteal cells to an autoimmune-type MHC-mediated response during luteal regression.

The local inflammation that occurs concurrently with autoimmune diseases is often attributed to pro-inflammatory cytokines produced by T_{h1} cells. The mRNAs for several pro-inflammatory T cell-derived cytokines, and in some cases the proteins themselves, are present in the CL [5,42-46]. The presence of T cell-derived cytokines in luteal tissue suggests that the T lymphocytes present within the tissue are activated. Activated T lymphocytes produce IFN-γ and TNF-α, which increase expression of class I and class II MHC molecules on luteal cells, as well as inhibit progesterone production [47,48]. Thus, a positive feedback loop of antigenic peptide presentation and T cell activation could occur to facilitate the rapid demise of the tissue that occurs during luteolysis.

The Role of Costimulation In T Cell Activation

The presence of class I and class II MHC molecules on the surface of a cell allows the cell to interact with CD8+ and CD4+ T lymphocytes, respectively. However, there are two possible outcomes of MHC-mediated cellular interactions with T cells. In one instance, binding of MHC molecules to the TCR can occur in the absence of accompanying interactions between additional cell surface molecules. In this case an inactive state known as anergy will be induced in the T cells [49,50]. Induction of anergy is one means by which tolerance to antigens in peripheral tissues is induced, thus avoiding an autoimmune response [51]. Anergic T cells are prevented from carrying out their effector functions (cytokine secretion in the case of CD4+ T cells; cytotoxic activity in the case of CD8+ cells).

Alternatively, MHC-TCR ligation can occur in conjunction with a second interaction known as costimulation. Costimulatory signals are delivered to T cells by the cell surface proteins B7-1 and/or B7-2, also known as CD80 and CD86, respectively [52-54]. These ligands, when present on the antigen presenting cell surface, bind to the CD28 cell surface molecule on T cells and provide the costimulatory signal that promotes T cell survival [55] and induces T cell activation and clonal expansion [49,52,56], allowing the T cell to carry out its effector functions.

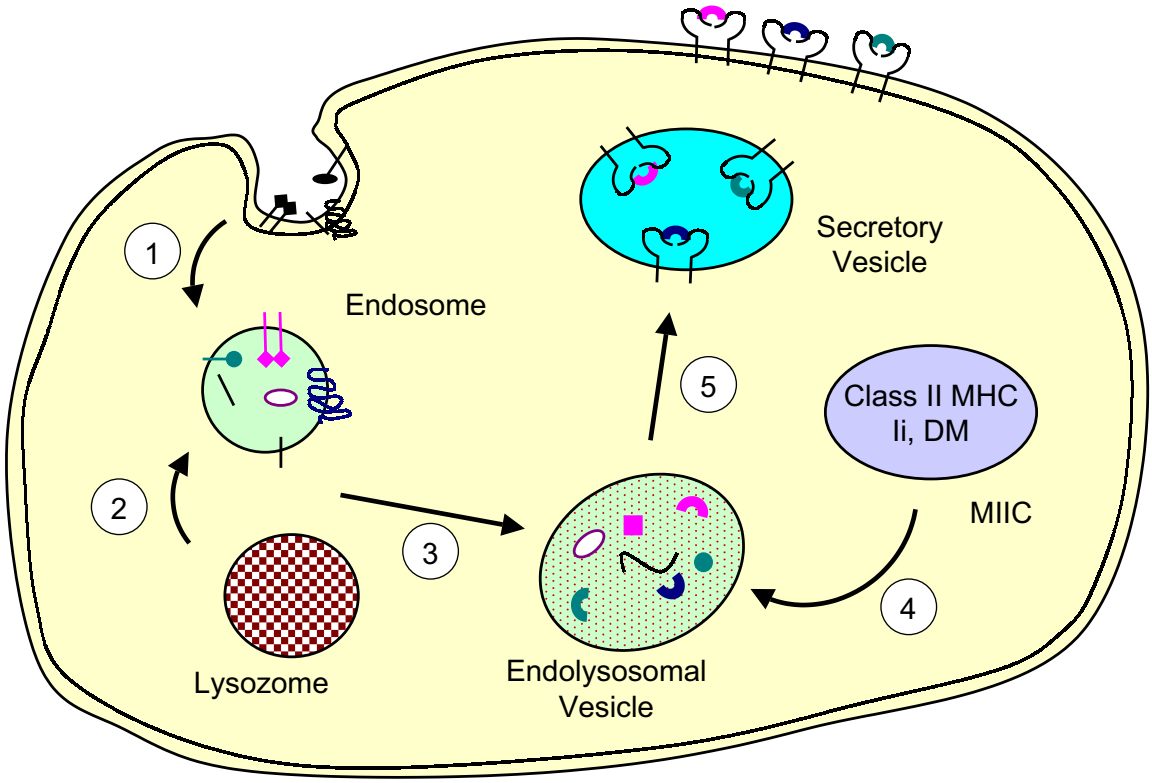

Figure 2
Schematic representation depicting processing of antigens presented by class II MHC molecules. 1) Extracellular and integral membrane proteins are internalized into endosomes via endocytosis. 2) Lysozomes fuse with endosomes. 3) Proteolytic degradation of endocytosed proteins occurs in the endolysosomal vesicle, resulting in the generation of antigenic peptides. 4) A specialized subcellualr organelle containing the class II MHC molecules, invariant chain, and DM fuses with the endolysosomal vesicle. This results in proteolytic degradation of invariant chain to CLIP. DM then catalyzes removal of clip, and the empty class II MHC molecules then bind antigenic peptides. 5) Class II MHC-antigenic peptide complexes are then exported to the cell surface, for presentation of antigenic peptide to $CD4^+$ T cells.

Therefore, while generation of sets of self-derived peptides capable of binding to MHC molecules and stimulating the activation of self-reactive T cells may predispose cells and tissues to an autoimmune response, the absence of a costimulatory signal can result in induction of tolerance to a tissue or cell type rather than activation of lymphocytes and induction of an immune response [57].

We recently demonstrated the expression of CD80 and CD86 in bovine luteal tissue. Similar to the pattern of DMα and DMβ expression, steady-state concentrations of CD80 and CD86 mRNA were greater in the bovine CL during midcycle as compared with early CL [58]. In functional studies, antibodies against CD80 or CD86 inhibited luteal cell-stimulated proliferation of T cells. These data indicate that bovine luteal cells express functional costimulatory molecules, which enable them to provide the costimulatory signal necessary for activation of T cells.

Conclusions

From the observation that expression of MHC molecules changes with functional state of the CL, it may be inferred

that these glycoproteins have a role in luteal physiology. Since class II MHC molecules increase during luteolysis and are suppressed during maternal recognition of pregnancy, it is likely that they are involved in luteal regression. Presentation of peptides in the context of MHC molecules would result in activation of T lymphocytes, with subsequent release of pro-inflammatory cytokines and cytolysis. Luteal tissue contains the intracellular proteins that are necessary for processing and presentation of antigenic peptides (LMP 7, LMP 10, Ii, DM), and the cell surface molecules necessary for costimulation (CD80, CD86) are also expressed. Further, these components are all apparently quite functional, since luteal cells are potent stimulators of T cell proliferation. Collectively, these events closely resemble those that occur in tissues undergoing autoimmune responses. Thus, we propose that the progression of luteolysis involves a localized autoimmune response involving MHC-mediated antigen presentation to T lymphocytes. The exact identity of the antigen-presenting cells is yet to be determined. Finally, it must also be recognized that the role of MHC molecules on luteal cells may be something other than to promote luteal regression. An alternative hypothesis is that MHC molecules are present in the CL to promote tolerance, particularly in the event of pregnancy. Clearly, the story of MHC molecules in the CL is just beginning to unfold.

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