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Autoimmunity and antigenic targets in ovarian pathology

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The involvement of autoimmune mechanisms in premature ovarian failure has been put forward by numerous investigators. In various other ovarian pathologies, such as idiopathic infertility, polycystic ovary syndrome, or endometriosis, similar mechanisms have been suggested. However, the exact role of autoimmunity in the pathophysiology of these diseases still remains controversial. The diagnosis of autoimmune ovarian disease relies on several clinical, biological and histological findings, but special interest has been focused on antiovarian autoantibodies. The search for these antibodies has been undertaken by several authors and yielded somewhat conflicting results which might be conditioned by methodological differences and by the multiplicity of potential immune targets. These targets, which comprise various steroidogenic enzymes, gonadotrophins and their receptors, the corpus luteum, zona pellucida and oocyte, are reviewed. Further investigation of these targets is required to improve the diagnostic tools that will lead to a precocious and reliable diagnosis of autoimmune ovarian disease, an appropriate clinical surveillance as well as the selection of patients who may benefit from immune-modulating therapy and possibly recover ovarian function and fertility.

Key words: antigenic targets/autoimmunity/ovary/premature ovarian failure

Introduction

The human ovary can be the target of an autoimmune attack in various circumstances, including several organ-specific or systemic autoimmune diseases. Clinically, the ensuing ovarian dysfunction often results in premature ovarian failure (POF), but other pathologies involving the ovaries, such as unexplained infertility, polycystic ovary syndrome (PCOS) and endometriosis have been associated with antiovarian autoimmunity (Luborsky, 2002).

The diagnosis of an autoimmune mechanism in these pathologies has relied for a long time on the detection of antiovarian autoantibodies, but recently special attention has also been focused on the cellular component of the autoimmune response (Melner and Feltus, 1999). However, little is known about the molecular targets of the autoimmune effectors, and very few autoantigens have been formally identified (Hoek *et al*., 1997).

The search for antiovarian antibodies has been undertaken in numerous studies, especially in patients with POF, but their results still remain conflicting, partly because of differences in the methods used for their detection. Nevertheless, the localization of these antibodies by indirect immunofluorescence initially enabled the identification of their targets at the cellular level, whereas in more recent biochemical approaches, some of these targets were further characterized at the molecular level.

The present paper reviews the prevalence, the clinical and biological significance of antiovarian autoantibodies as well as their cellular and molecular targets, as far as they have been characterized until now.

Autoimmunity in ovarian diseases

Autoimmune POF

POF is characterized by the loss of ovarian functions before the age of 40 years; its prevalence is ~1% of women. Classically, POF has a genetic, enzymatic, infectious, or iatrogenic aetiology (Anasti, 1998; Kalantaridou *et al*., 1998). In most cases, however, no precise cause can be identified, and these forms are referred to as idiopathic. The possibility of an autoimmune mechanism in some cases of POF relies on clinical and therapeutic observations as well as on immunological and histological findings.

Clinical features of autoimmune POF

Association with autoimmune diseases. It has long been recognized that POF could be associated with nearly all organ-specific autoimmune diseases (Table I). The best known, although not the most frequent of these associations, is adrenal autoimmunity. The relationship between ovarian failure and adrenal disease was first suggested 70 years ago in two patients with Addison's disease and atrophic ovaries (Duff and Bernstein, 1933). This association has been further established in several clinical case reports from the early 1950s on, and in some of these cases, there were even other endocrine diseases associated, such as hypothyroidism or diabetes

Table I. Autoimmune diseases associated with POF

Authors	Frequent associations	Occasional associations	
		Organ-specific diseases	Non organ-specific diseases
Crispell and Parson, 1952	Thyroid diseases	Hypoparathyroidism	Lupus erythematosus
Guinet and Pommateau, 1954	APS-II	Myasthenia gravis	Idiopathic thrombocytopenia
Rupp and Paschkis, 1955	APS-I	Diabetes mellitus	Haemolytic anaemia
Turkington and Lebovitz, 1967	Addison's disease	Pernicious anaemia	Sjögren's syndrome
Vazquez and Kenny, 1973		Vitiligo	
Rebar *et al*., 1982		Alopecia areata	
Coulam, 1983		Crohn's disease	
Aiman and Smentek, 1985		Ulcerative colitis	
Alper and Garner, 1985		Coeliac disease	
LaBarbera *et al*., 1988		Glomerulonephritis	
Betterle *et al*., 1993		Rheumatoid arthritis	
Kim *et al*., 1995		Juvenile idiopathic arthritis	
Conway *et al*., 1996		Primary biliary cirrhosis	
Betterle and Volpato, 1998		Multiple sclerosis	
Packham and Hall, 2003			

APS = autoimmune polyglandular syndrome.

mellitus (Crispell and Parson, 1952; Guinet and Pommateau, 1954; Rupp and Paschkis, 1955; Turkington and Lebovitz, 1967).

Later on, numerous other organ-specific autoimmune diseases have been found to be associated with POF, such as Hashimoto thyroiditis, Graves' disease, myasthenia, rheumatoid arthritis, pernicious anaemia, vitiligo, Crohn's disease, coeliac disease, multiple sclerosis as well as some non-organ-specific disorders, such as systemic lupus erythematosus or idiopathic thrombocytopenia (De Moraes-Ruehsen *et al*., 1972; Rebar *et al*., 1982; Coulam, 1983; LaBarbera *et al*., 1988; Betterle *et al*., 1993; Dal Pra *et al*., 2003).

As has already been recognized in the earliest above-mentioned reports, POF may be associated with several autoimmune diseases in the same patients. Such cases are now referred to as autoimmune polyglandular syndrome (APS). Three different types of this syndrome have been described since the early 1980s:

(i) APS-I, also called APECED (autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy) is a rare autosomal recessive disease caused by mutations in the *AIRE (autoimmune regulator)* gene (Nagamine *et al*., 1997). The diagnosis is generally made in childhood, because of adrenal and parathyroid autoimmune disease, frequently associated with cellular immune deficiencies, causing chronic superficial candidiasis, as well as with ectodermal defects, such as dental hypoplasia or ungueal dystrophies. The prevalence of POF in this type of APS is ~39% at the age of 15 years and 72% at 40 years (Perheentupa, 2002).

(ii) APS-II, also called Schmidt–Carpenter syndrome, includes adrenal and thyroid autoimmunity as well as type I diabetes. APS-II is more frequent than APS-I, but clinical signs only appear in the adult. Prevalence of ovarian failure in this type is only ~10% at the age of 40 years (Schatz and Winter, 2002). Unlike APS-I, this type is not associated with a particular gene but with different alleles of the MHC (HLA-DR and DQ) that confer a particularly high susceptibility for autoimmune diseases (Maclaren *et al*., 2001).

(iii) APS-III is quite similar to APS-II, except that there is no Addison's disease, but other autoimmune diseases, such as anaemia perniciosa or vitiligo are often associated (Schatz and Winter, 2002).

The prevalence of associated clinical autoimmune disease in POF patients has been evaluated quite variously: ~10–20% in some studies (Coulam, 1983; Aiman and Smentek, 1985; Conway *et al*., 1996), nearly 40% in others (Alper and Garner, 1985; Betterle *et al*., 1993), and up to 55% (De Moraes-Ruehsen *et al*., 1972). Among all autoimmune diseases associated with POF, thyroid disorders are definitely the most common and can be detected in 12–33% of the patients (De Moraes-Ruehsen *et al*., 1972; Rebar *et al*., 1982; Alper and Garner, 1985; Betterle *et al*., 1993). In 18% of the cases, there is a familial history of autoimmune thyroid disease (Alper and Garner, 1985). Therefore a complete record of personal and familial history and routine screening of thyroid function have to be performed in a patient with POF.

The second most frequent autoimmune associations in POF patients are APS II and APS I (Kim *et al*., 1995). The natural history of these syndromes is quite variable: POF may be detected either before, after or simultaneously with the onset of the other autoimmune disorders. However, as far as Addison's disease is concerned, POF frequently precedes the adrenal disease, sometimes for several years (Turkington and Lebovitz, 1967; Kim *et al*., 1995), which emphasizes the need for adrenal function testing and precocious detection of this potentially life-threatening disease in POF patients. The benefit of performing a wider endocrine function setting and autoantibody screening in the absence of clinical symptoms, as has been recommended earlier (Rebar *et al*., 1982), still remains questionable, except for thyroid disease and diabetes mellitus, because of the very low frequency of the other autoimmune associations (Kim *et al*., 1997).

However, some authors have tested idiopathic POF patients' sera for a multitude of organ-specific and non-organ-specific antibodies. The percentage of patients with at least one autoantibody in their serum was between 40 and 92%, and correlated with the number of antibodies tested (Miyake *et al*., 1987; Mignot *et al*.,

Table II. Corticosteroid therapy in POF patients

Authors	Study design	Patients	Age	Associated AD	Ovarian biopsy	AOA	Corticosteroids	Issue
Coulam *et al*., 1981	CR	1	22	Adrenal	Oophoritis	+	Prednisone 40 mg/day, 7 days; prednisone 20 mg/day, 7 days; hydrocortisone 30 mg/day, 6 months	RM after 1 month; 2 menstrual cycles; no pregnancy
Rabinowe *et al*., 1986	CR	1	32	None	Oophoritis	+	Prednisone 40 mg/day, 6 months	RM after 1 month; 10 cycles, no pregnancy
Cowchock *et al*., 1988	CR	1	43	Adrenal	n.a.	n.a.	Prednisone 7.5 mg/day and fludrocortisone 0.5 mg/day	RM and normal pregnancy
Luborsky *et al*., 1990	CR	2	24	Diabetes; Graves'	n.a.	+	Methylprednisolone, 96 mg/day; 10 days, taper during 6 days	RM and normal pregnancy
			33	None	n.a.	+	Methylprednisolone, 96 mg/day; 10 days, taper during 6 days	RM and normal pregnancy
Corenblum *et al*., 1993	UC	11	20–38	Thyroid (4); RA (1)	n.a.	n.a.	Prednisone 100 mg/days, 2 weeks	RM and normal pregnancy in 2/11 patients; no effect in 9/11
Blumenfeld *et al*., 1993	UC	15	20–41	Thyroid (6); ITP (1)	n.a.	n.a.	Fluorocortolone 10 mg/day, 2 weeks and triptoreline, hMG	14 pregnancies in 8/15 patients; 10 healthy infants
Kalantaridou *et al*., 1999	CR	2	29	n.a.	Oophoritis	n.a.	Prednisone 11 mg/day, 16 weeks	RM, 6 cycles, no pregnancy
			36	Thyroid	n.a.	n.a.	Dexamethasone 2 mg/day, 9 months	No RM, right knee osteonecrosis
Van Kasteren *et al*., 1999	PC, R	35	18–40	None	n.a.	n.a.	Dexamethasone 9 mg/day, 1 week, taper during 8 days and hMG	No ovulation, no pregnancy in any patient

AD = autoimmune diseases; AOA = antiovarian antibodies; CR = case report; UC = uncontrolled study; PC, R = placebo-controlled, randomized study; RM = resumption of menses; RA = rheumatoid arthritis; ITP = idiopathic thrombocytopenia; n.a. = data not available.

1989a; Belvisi *et al*., 1993; Blumenfeld *et al*., 1993). This extensive screening appears of low value in the diagnosis of autoimmune forms of POF because of a low specificity, but it illustrates further the frequency of autoimmune disorders in this ovarian pathology.

Because of the particular association with Addison's disease and the clinical features described above, three different situations have to be distinguished: POF associated with adrenal autoimmunity; POF associated with nonadrenal autoimmunity; and isolated, idiopathic POF. Clearly, in the latter situation, the absence of associated disease cannot exclude an autoimmune mechanism, as will be discussed later.

Effects of immunosuppressive therapies. A possible effect of immunosuppression with corticosteroids on the resumption of ovarian function in POF patients has been suggested by several authors and considered as a proof of the autoimmune aetiology in these cases (Table II). In two patients with secondary amenorrhoea, elevated gonadotrophins and perifollicular lymphocytic infiltrate, menses resumed after 1 month of corticosteroid therapy, but no pregnancy could be achieved (Coulam *et al*., 1981; Rabinowe *et al*., 1986). Another patient who had been treated with estrogen replacement therapy because of POF for >15 years, developed Addison's disease and presented a spontaneous and uneventful pregnancy after 1 year of corticosteroid replacement therapy (Cowchock *et al*., 1988). In another report, two patients with documented POF became pregnant and delivered a healthy infant after high dose corticotherapy, but in both cases, POF resumed after delivery (Luborsky *et al*., 1990). More recently, a patient with secondary amenorrhoea and documented oophoritis resumed spontaneous menstrual bleeding six times and ovulated four times during a low dose corticosteroid treatment, but without getting pregnant (Kalantaridou *et al*., 1999). After IVF, a pregnancy and delivery has also been obtained under corticosteroid treatment in a patient with antiovarian autoimmunity who had already experienced two unsuccessful IVF attempts (Barbarino-Monnier *et al*., 1995). Besides these case reports, two uncontrolled trials have been carried out among chromosomally normal POF patients. In one study, two of 11 idiopathic POF patients receiving high dose corticosteroids for 15 days resumed ovarian function and became pregnant (Corenblum *et al*., 1993). In the other trial, 15 POF patients selected for having various autoimmune markers were treated with hMG and corticosteroids after pituitary desensitization with a GnRH agonist. Eight of them became pregnant at least once and in total, 14 pregnancies were obtained and 10 babies were born (Blumenfeld *et al*., 1993). All of these pregnancies were obtained within the first 3 months after the onset of treatment. The authors concluded that patients with autoimmune POF had a better fertility prognosis than unselected patients.

However, it should be highlighted that none of these studies yielded a definite proof of the efficacy of corticosteroids, as, on one hand, spontaneous pregnancies have been reported in POF patients in the absence of any treatment (Rebar *et al*., 1982), and, on the other hand, there has been, to our knowledge, no randomized trial with well-selected autoimmune POF patients. The only randomized, placebo-controlled trial using corticoster-

oids and hMG in 36 idiopathic POF patients for 2 weeks did not show any positive effect as none of these patients became pregnant, nor even ovulated under the treatment (Van Kasteren *et al*., 1999). In fact, the presence of specific antiovarian antibodies has not been assessed in these patients. This further illustrates the need for accurate diagnostic tools in order to analyse the effect of corticosteroids in a selected population of well-defined autoimmune POF patients.

Immunological features of autoimmune POF

Humoral immunity. The detection of autoantibodies directed against various ovarian targets strongly supports the hypothesis of an autoimmune aetiology of POF. The first reports on such antibodies included mainly patients with POF and an associated adrenal autoimmune disease. These patients had antibodies that recognized several types of steroid-producing cells of the adrenal cortex, testis, placenta and ovary and were therefore called steroid cell antibodies (SCA) (Irvine *et al*., 1968; Sotsiou *et al*., 1980). The prevalence of SCA depends on the clinical features: they can be detected in ~60% of APS-I patients and 25–40% of APS-II patients (Hoek *et al*., 1997), but the highest prevalence, i.e. 78–100%, has been shown in patients with both Addison's disease and POF (Sotsiou *et al*., 1980; Betterle *et al*., 1993). In a long-term study, it has been shown that 33–43% of normally cycling women with polyendocrinopathy and SCA would develop ovarian failure within 8–15 years (Ahonen *et al*., 1987; Betterle *et al*., 1993). The presence of these antibodies is thus a risk factor for POF.

In patients whose POF is associated with autoimmune pathologies other than Addison's disease (Betterle *et al*., 1993; Falorni *et al*., 2002; Dal Pra *et al*., 2003), as well as in isolated POF (De Moraes-Ruehsen *et al*., 1972; Betterle *et al*., 1993; Falorni *et al*., 2002; Dal Pra *et al*., 2003), the prevalence of SCA remains <10%. Many other antiovarian antibodies have been detected in these cases and numerous publications have dealt with this subject over the last 30 years. Despite this considerable scientific work, the detection of antiovarian antibodies still produces conflicting results and until now, neither the specificity nor the diagnostic significance of these antibodies has been unanimously established. One of the reasons for these discordances is the diversity of the detection methods as well as the heterogeneity of the patient and control groups in the different studies.

Indirect immunofluorescence is the first described and most common method used for the detection of antiovarian antibodies in serum. It is usually performed by trained laboratory staff on frozen sections of human or, more often, animal ovaries. It shows the localization of the antibodies in the various histological compartments of the ovary, as will be described later. However, the diverse origin of the tissue sections which include human, non-human primate, bovine, porcine, rat, guinea-pig and rabbit ovaries may explain the variations of the results of the prevalence, localization and specificity of the detected antibodies. But even with immunofluorescence on human ovary sections, the prevalence of antiovarian antibodies in the serum of patients with POF may vary between 2% (Ho *et al*., 1988) and 50% (Damewood *et al*., 1986). Moreover, tissue sections may originate from women or animals at different ages or at different periods of the menstrual cycle. Finally, there is no consensus about the inclusion criteria for patients as well as for control subjects in the different studies. Thus, the percentage of healthy control subjects with detectable antiovarian antibodies may be up to 38% in some studies (Novosad *et al*., 2003).

Since the late 1980s, immunoenzymatic methods, especially enzyme-linked immunosorbent assays (ELISA) have been developed. In these techniques, homogenized human or animal ovarian tissues are used as a source of ovarian antigens and results can be quantified. Blending ovarian tissues from different women at various ages and periods of the menstrual cycle provides a large panel of ovarian antigens and allows an economical use of this precious material. Altogether, ELISA detection of antiovarian antibodies yields more homogeneous results than immunofluorescence studies (Table III). Between 30 and 67% of POF patients have such antibodies in their serum, whereas only 0–5% of healthy control subjects are found to be positive (Luborsky *et al*., 1990; Wheatcroft *et al*., 1994; Fénichel *et al*., 1997; Wheatcroft *et al*., 1997a). Nevertheless, the specificity of these ELISA-detected antibodies remains questionable in some cases because of a cross-

Table III. Enzyme-linked immunosorbent assay detection of antiovarian autoantibodies (AOA)

Authors	Antigenic substrate	Patients	AOA in idiopathic POF	AOA in POF with associated AD	AOA in other clinical situations	AOA isotypes	AOA in controls
Luborsky *et al*., 1990	Pooled ovarian extract				History of pelvic surgery		
	Oocytes (failed IVF)	45	16/24	8/12	7/9	n.a.	0/10
Wheatcroft *et al*., 1994	Ovarian extract from 2 ovaries	41			Turner and iatrogenic POF	n.a.	
			4/26 (ovary 1)	2/6 (ovary 1)	3/8 (ovary 1)		2/33 (ovary 1)
			16/26 (ovary 2)	2/6 (ovary 2)	7/9 (ovary 2)		2/41 (ovary 2)
Wheatcroft *et al*., 1997a	Pooled ovarian extract	42	9/30	4/12		n.a.	0/38
Fénichel *et al*., 1997	Pooled ovarian extract	46	22/38	5/8		IgG 20/27 IgA 8/27 IgM 9/27	4/23

POF = premature ovarian failure; AD = autoimmune diseases.

reaction with tubal (Wheatcroft *et al*., 1994) or even muscular antigens (Wheatcroft *et al*., 1997a). Moreover, their clinical significance is not always obvious, as they can be detected in patients with iatrogenic POF or Turner syndrome (Wheatcroft *et al*., 1994).

Cellular immunity. Abnormalities of the cellular immunity, i.e. T lymphocytes, macrophages and dendritic cells, also play an important role in autoimmune reactions, particularly in the development of autoimmune lesions. Some of these abnormalities have been recently described in POF and thus support the autoimmune mechanisms of this disease.

As in other autoimmune diseases, the absolute count and percentage of peripheral blood T-lymphocytes, especially CD4+ T cells, has been found to be increased in patients with POF (Mignot *et al*., 1989b). Flow cytometry has been used by several authors for further immunophenotyping peripheral lymphocyte subsets in POF patients, but some conflicting results have been obtained. Thus it has been shown that POF patients had low levels of CD8+/CD57+ T cells (cytotoxic T lymphocytes) and an overall increase of the CD4+/CD8+ ratio (Miyake *et al*., 1987; Chernyshov *et al*., 2001), which is consistent with the above-mentioned increase of the CD4+ count. However, no difference in the CD4+/CD8+ ratio was reported in another study (Rabinowe *et al*., 1989). A third group also described a decrease of this ratio in POF patients, yet suggested that this feature could also be caused by chronic hypoestrogenism (Ho *et al*., 1993).

Increased circulating B-cells in POF patients have been reported to be independent of serum estrogen levels (Hoek *et al*., 1995) and immunophenotyping demonstrated a high percentage of CD19+/CD5+ cells (B2 cells involved in autoimmunity) in POF patients (Chernyshov *et al*., 2001). Activated T cells also seem to be increased in POF as it has been shown that 35–50% of these patients present a higher expression of the MHC class II molecules, especially HLA-DR, on their T lymphocytes than healthy control subjects (Rabinowe *et al*., 1989; Nelson *et al*., 1991).

The alteration of cellular immunity has also been illustrated by a cutaneous candidine (derived from *Candida albicans*) delayed hypersensitivity test being negative in 50% of POF patients (Hoek *et al*., 1995). Finally, *in vitro* tests showed that blood monocytes from 20 to 46% of POF patients had an abnormal response to chemotactic agents (Pekonen *et al*., 1986; Hoek *et al*., 1993), whereas dendritic cells from 36% of the same patients presented a reduced capacity to aggregate with T-lymphocytes. Similar findings have been reported in other autoimmune diseases, such as type I diabetes or Graves' disease (Hoek *et al*., 1993).

Finally, the number as well as the activity of natural killer (NK) cells seemed to be reduced in POF patients (Pekonen *et al*., 1986; Hoek *et al*., 1995). The coexistence of an autoimmune ovarian inflammation and an impaired cellular immune response further illustrates the complex defects of immune regulation in autoimmune ovarian disease.

The involvement of cellular immunity in the pathogenesis of autoimmune ovarian disease has also been investigated in animal models, such as murine post-thymectomy oophoritis and active immunization with ovarian extracts. These experimental diseases cannot be described in detail here, but it should be mentioned that the autoimmune oophoritis which develops in these models can be transferred in some cases to healthy recipients by peripheral, lymph node, or splenic T-lymphocytes (Damjanovic, 1991; Tung *et al*., 2001).

Histological findings in POF patients

Histological examination of ovaries from POF patients shows either a complete loss of ovarian follicles or the persistence of more or less abundant follicles. The latter cases are called 'follicular forms' and represent ~40% of POF patients (Hoek *et al*., 1997). This is in accordance with ultrasound studies which revealed residual follicular structures in 41–60% of patients presenting clinical and biological signs of POF (Mehta *et al*., 1992; Conway *et al*., 1996).

In those cases where POF is associated with adrenal autoimmunity, histological examination almost always confirms the persistence of ovarian follicles with characteristic signs of an autoimmune oophoritis: follicles are infiltrated by inflammatory cells, including lymphocytes, plasma cells and macrophages. The intensity of the inflammatory infiltrate seems to increase with the maturation stage of the follicles, culminating in pre-ovulatory follicles and corpora lutea, whereas primordial and primary follicles are spared as described in several case reports (Coulam *et al*., 1981; Russell *et al*., 1982; Gloor and Hurlimann, 1984; Rabinowe *et al*., 1986; Sedmak *et al*., 1987; Wolfe and Stirling, 1988; Biscotti *et al*., 1989; Lonsdale *et al*., 1991; Suh, 1992) and confirmed in a series of 12 patients (Bannatyne *et al*., 1990). Immunohistochemical staining techniques have revealed infiltrating lymphocytes being T-cells (CD4+ CD8+), which is consistent with a potential role of T-lymphocytes in autoimmune ovarian disease (Sedmak *et al*., 1987).

In contrast, only a few patients whose POF is not associated with adrenal autoimmunity presented with this typical oophoritis among 215 cases of POF from 18 studies published between 1965 and 1991, where histological oophoritis was documented in only six of them (Hoek *et al*., 1997). However, the rarity of inflammatory infiltrates in these patients does not exclude the possibility of an autoimmune mechanism. Follicular depletion could be the consequence of non-autoimmune aetiologies, but it might also be the final stage of an autoimmune disease, where inflammation has ceased as all autoantigens have been eliminated. Thus the natural history of POF has to be taken into account when interpreting results from those patients.

Autoimmune forms of other ovarian pathologies

Antiovarian autoantibodies have been detected in 33–61% of patients with unexplained infertility, suggesting that this pathology may represent an early stage of autoimmune ovarian failure (Luborsky *et al*., 1999a). These antibodies actually were not correlated with serum FSH or inhibin B levels and therefore could be considered as independent markers of autoimmune ovarian disease. Furthermore, as in other autoimmune pathologies (such as type 1 diabetes mellitus and thyroiditis), antiovarian antibodies may appear months or years before the onset of clinical symptoms (Wheatcroft *et al*., 1997b; Luborsky *et al*., 2000), thus they could predict future ovarian failure in women with unexplained infertility. The above-mentioned results are in accordance with an earlier report of patients presenting with 'occult ovarian failure', where 40% had antiovarian antibodies. This state was defined by the authors as an association of impaired response to an ovulation induction treatment, elevated FSH levels, but still regular menses,

and thus could represent a more evolved stage of the ovarian disease (Cameron *et al*., 1988).

An autoimmune mechanism has also been suggested in some cases of polycystic ovary syndrome (PCOS). The heterogeneity of PCOS and of antibody tests leads to conflicting results. Histopathological features of autoimmune oophoritis with a cystic aspect associated with anti-ovarian serum antibodies have been reported (Bannatyne *et al*., 1990; Lonsdale *et al*., 1991; Suh, 1992). Antiovarian antibodies were detected in the serum of about half of PCOS patients (Van Gelderen and Gomes dos Santos, 1993; Fénichel *et al*., 1999) but these results could not be confirmed by others (Rojanski *et al*., 1997; Luborsky *et al*., 1999b). These discrepancies could be explained in part by the use of different antigenic substrates in these studies: granulosa cells for Van Gelderen and Gomes dos Santos, human ovary extract for Fénichel, ovarian follicle theca interna for Rojanski and 'microsomal' antigens for Luborsky.

The mechanism of infertility in endometriosis is not well understood. Because endometriosis was shown to be associated with autoantibodies and/or other autoimmune diseases in up to two-thirds of patients, an autoimmune mechanism has been hypothesized (Gleicher *et al*., 1987). Mathur *et al*. (1982) reported the presence of antiendometrial antibodies in 100% and antiovarian antibodies in 62% of 13 patients with endometriosis. A majority of patients with antiovarian antibodies had ovarian endometrioma. In a larger study, however, this proportion was not as high (Halme and Mathur, 1987), whereas other authors could not detect any antibodies (Switchencko *et al*., 1991). The presence of antiovarian antibodies in the peritoneal fluid rather than in the serum of endometriosis patients could be consistent with a role of the local immune system in the pathogenesis of this pathology (Szczepanska *et al*., 1997), but in an earlier study, there was no difference in the prevalence of peritoneal fluid antiovarian antibodies between patients with endometriosis and control subjects (Halme and Mathur, 1987). Despite these apparently conflicting results, endometriosis shares a lot of common features with other autoimmune diseases, which have been recently reviewed elsewhere (Nothnick, 2001).

Finally, the evaluation of antiovarian autoimmunity could be a tool of prognosis for infertility treatments, especially in IVF. In IVF patients, the presence of these autoantibodies could predict low estradiol responses to FSH (Meyer *et al*., 1990; Luborsky *et al*., 2002), lower fertilization rate (Narayanan *et al*., 1995; Moustafa *et al*., 1997) and a lower pregnancy rate (Barbarino-Monnier *et al*., 1991; Narayanan *et al*., 1995; Geva *et al*., 1996; Luborsky and Pong, 2000). Some of these studies suggested that the trauma of the follicular puncture may have caused or enhanced the formation of antiovarian antibodies (Gobert *et al*., 1990; Barbarino-Monnier *et al*., 1991; Gobert *et al*., 1992; Monnier-Barbarino *et al*., 2003) rather than exogenous hormonal stimulation (Moncayo *et al*., 1989).

In conclusion, autoimmune mechanisms may be suspected in various clinical situations of ovarian disease. Diagnosis of autoimmune aetiology remains difficult and relies on several clinical, immunological and histological features that should be investigated in these patients. The involvement of autoimmunity has been most extensively studied in POF: cases of POF associated with antiadrenal autoimmunity represent a homogeneous and well-characterized subgroup of ovarian failure, whereas in other forms of this disease, there is a large diversity in clinical, immunological and histological features. Therefore, the overall proportion of autoimmune forms of POF has been estimated at between 20% (Wheatcroft *et al*., 1994) and 70% (Luborsky, 2002). Besides POF, other ovarian diseases are candidates for an autoimmune pathophysiology: unexplained infertility, polycycstic ovary syndrome and endometriosis. However, the aetiological significance of autoimmunity in these pathologies still remains controversial.

Antigenic targets of the antiovarian autoimmune reactions

Little is known about the precise nature of the ovarian antigens that are recognized by antibodies and immune cells in autoimmune diseases of the ovary. As to the cellular targets, the immune reaction can be directed against either the somatic component of the ovarian follicle, i.e. mainly the granulosa and the thecal layer, or the germinal component, i.e. the oocyte itself, or the zona pellucida which separates these two components. In some of these cellular sites, molecular targets have been identified. The following review of these immune targets is based on the histological localization of antiovarian antibodies by immunofluorescence staining.

Targets of SCA

Autoantibodies directed against steroid hormone-producing cells have initially been described by Anderson *et al*. (1968) in two patients with Addison's disease. Irvine *et al*. (1968) then detected these antibodies in 10 patients with Addison's disease, five of them presenting with POF. The serum of these patients contained antibodies that recognized the adrenal cortex, placental trophoblast, internal theca and interstitial cells of the gonads, as assessed by indirect immunofluorescence on human and rabbit tissue sections (Table IV). In the ovary, internal theca was the preferential localization, but the corpus luteum and sometimes granulosa cells also showed immunostaining (Irvine et al., 1968, 1969).

The same technique using human and simian tissues allowed Sotsiou *et al*. (1980) to confirm these results in a larger series of patients, including 115 cases of Addison's disease and 37 patients with other autoimmune pathologies. The overall prevalence of SCA was ~30%, but in patients who also presented with POF, all of them had SCA in their serum. By contrast, in another series of 29 patients with idiopathic POF, almost exclusively those who had an additional autoimmune disease (16 of them) showed SCA, whereas only one of the 13 patients with isolated POF had these antibodies (De Moraes-Ruehsen *et al*., 1972). This study is consistent with the results of Betterle *et al*. (1993) who detected SCA in 78% of patients with POF associated with Addison's disease, 10% of patients associated with non-adrenal autoimmune disease, and only 6.5% of patients with isolated POF. Furthermore two recent studies showed SCA to be present in 73–87% of patients with Addison's disease and POF, 0–8% of POF patients with other autoimmune diseases, and 0–10% of patients with isolated POF (Falorni *et al*., 2002; Dal Pra *et al*., 2003).

The particular localization of SCA has led to the hypothesis that they could recognize some steroidogenic enzymes. In Addison's disease, anti-adrenal antibodies (ACA) have been detected by indirect immunofluorescence in the cytoplasm of adrenal cortex

Table IV. Principal features of anti-steroid cell antibodies (SCA)

Authors	Prevalence (%)				
	ADD	POF with ADD	POF with NA-AD	Isolated POF	Healthy controls
Irvine *et al*., 1968	0	83	n.a.	n.a.	0
De Moraes-Ruehsen *et al*., 1972	n.a.	100	33[a]	8	0
Sotsiou *et al*., 1980	22	100	n.a.	n.a.	0
Betterle *et al*., 1993	20	78	10	6.5	0
Falorni *et al*., 2002	15	87	0	0	0
Dal Pra *et al*., 2003	n.a.	73	8	10	0

Histological targets: adrenal cortex (all three layers), placental trophoblast, internal theca; corpus luteum, granlosa layer, Leydig cells (Irvine et al., 1968; Irvine et al., 1969; Sotsiou et al., 1980).
Molecular targets: P450-cytochrome C side chain cleavage (SCC), P450-cytochrome C 17α-hydroxylase (17OH), 3β-hydroxysteroid dehydrogenase (3-HSD), unidentified 51 kDa autoantigen (Winqvist et al., 1993, 1995; Chen et al., 1996; Arif et al., 1996, 1999; Peterson et al., 1997; Reimand et al., 2000; Falorni et al., 2002).
ADD = Addison's disease; POF = premature ovarian failure; NA-AD = non-adrenal autoimmune diseases.
[a]One case out of three; n.a. = data not available.

cells (Anderson *et al*., 1957). Later on these ACA have been shown to recognize 21-hydroxylase, and specific anti-21-hydroxylase antibodies are still considered the best immunological marker of the disease (Baumann-Antczak *et al*., 1992; Winqvist *et al*., 1992). Subsequently, two other steroidogenic enzymes, P450-17α-hydroxylase (17OH) and P450-side chain cleavage (SCC), have been identified as antigenic targets in polyglandular autoimmune syndromes (Winqvist *et al*., 1993). The prevalence of antibodies against these enzymes is higher in APS-I than in APS-II or Addison's disease where anti-21-hydroxylase antibodies are predominant (Uibo *et al*., 1994).

In POF associated with Addison's disease, the prevalence of these antibodies, as determined by radiobinding assays with *in vitro* translated recombinant ^{35}S-labelled autoantigens, was 50 and 71% for anti-17OH and anti-SCC antibodies respectively (Falorni *et al*., 2002). However, in isolated POF or POF associated with non-adrenal autoimmune disease, antisteroidogenic enzyme antibodies were very rare or even absent, thus in all clinical situations, they were well correlated with SCA (Wheatcroft *et al*., 1994; Chen *et al*., 1996; Tanaka *et al*., 1997; Betterle *et al*., 1999; Falorni *et al*., 2002). The correlation between SCA and anti-17OH/anti-SCC antibodies suggested that 17OH and P450-SCC were actually the molecular targets of SCA (Chen *et al*., 1996). At present, most authors agree with this interpretation (Hoek *et al*., 1997; Falorni *et al*., 2002). Nevertheless, in ~10% of SCA positive patients, neither 17OH nor SCC antibodies were detected, which suggests that other autoantigens were recognized by SCA (Falorni *et al*., 2002). Thus, an unidentified 51 kDa autoantigen that has been detected in granulosa cells and placenta could be such an additional target of SCA (Winqvist *et al*., 1995).

Thus, another steroidogenic enzyme, 3β-hydroxysteroid dehydrogenase (3-HSD), which does not belong to the family of cytochrome P450 associated enzymes, could also be an autoimmune target. Indeed, anti-3-HSD antibodies have been detected by an immunoblotting technique in 21% of 48 patients with idiopathic POF (Arif *et al*., 1996). In this study, the authors found that anti-3-HSD antibodies had a higher diagnostic sensitivity than SCA antibodies for autoimmune POF, as only one of these unexplained POF patients had SCA. However, the specificity of anti-3-HSD antibodies was quite low, as they had also been detected in 23% of patients with type I-diabetes, 17% of patients with autoimmune thyroid disease and 5% of healthy control subjects. In a subsequent study, the same group showed that anti-3-HSD antibodies in POF patients were frequently associated with HLA-*DQB1* genotypes encoding aspartate at position 57 (*DQB1*0301*, *DQB1*0603*, and others), but these results did not reach statistical significance after correction for multiple analysis (Arif *et al*., 1999). Another group used a quantitative immunoprecipitation assay with recombinant, ^{35}S-radiolabelled 3-HSD, and showed that none of 46 patients with APS I, including 11 with associated POF, turned out to be positive for anti-3-HSD antibodies (Peterson *et al*., 1997).

In contrast with these studies, Reimand *et al*. (2000) found these antibodies in only one (2%) of 48 POF patients (six of whom had associated Addison disease), but also in 20% of patients with APS-I. More recently, in a similar study using ^{3}H-radiolabelled 3β-HSD, another group confirmed the rare occurrence of these antibodies in 81 POF patients (24 with Addison disease, 21 with other non-adrenal autoimmune disease, and 36 with isolated POF). Only 3.7% of them were found positive which was not statistically different from the control subjects (Falorni *et al*., 2002). In the two latter studies, patients with 3β-HSD antibodies were also positive for SCA. Therefore, it is possible that 3-HSD could be one of the immune targets of ovarian autoimmunity, but it remains questionable whether this enzyme is recognized by SCA. Anyway, the low frequency of anti-3β-HSD antibodies limits their clinical use as a marker of autoimmune ovarian disease.

In summary, steroidogenic enzymes represent autoimmune targets in the ovary, but their pathophysiological significance seems to be restricted to patients whose ovarian failure is associated with adrenal autoimmunity. In >90% of these cases, at least one of the three major antibodies, i.e. SCA, anti-17OH and anti-SCC antibodies, can be detected (Falorni *et al*., 2002). Therefore, these antibodies are very useful markers of ovarian failure in Addison's disease patients.

Gonadotrophin receptors as autoimmune targets?

The indirect immunofluorescence detection of autoantibodies on the surface of granulosa cells led to the hypothesis that

Table V. Detection of anti-gonadotrophin receptor autoantibodies

Authors	Patients	Patients with associated AD	Method	Test substrate	Positive results
Austin *et al*., 1979	14 POF	n.a.	LH-R binding of [^{125}I]hCG	Human CL	0/14
Chiauzzi *et al*., 1982	11 POF	6	FSH-R binding of human [^{125}I]hCG	Rat testis	2/11 (associated with myasthenia)
Tang and Faiman, 1983	9 POF	1	FSH-R/LH-R binding of bovine ^{125}I-FSH and bovine ^{125}I-LH	Bovine testis	1/9 (associated with AD)
Moncayo *et al*., 1989	30 endometriosis and infertility	n.a.	ELISA	Bovine CL (soluble and extractable antigen preparation); purified bovine LH/hCG-R	13/30
Van Weissenbruch *et al*., 1991	26 POF	10	FSH-induced granulosa cell DNA synthesis	Rat granulosa	21/26
			LH-induced ascorbic acid depletion	Rat CL	0/26
			LH-induced testosterone synthesis	Mouse testis	0/26
Wheatcroft *et al*., 1994	35 POF	9	ELISA	Bovine CL (soluble and extractable antigen preparation)	Not different from controls
Anasti *et al*., 1995	38 POF	17	FSH-induced progesterone synthesis; LH-induced cAMP synthesis	Transgenic cell lines expressing human FSH or human LH	0/38

AD = autoimmune disease; LH-R = LH receptor; FSH-R = FSH receptor; CL = corpus luteum; n.a. = data not available; ELISA = enzyme linked immunosorbent assay.

gonadotrophin receptors could be their targets (Damewood *et al*., 1986; Scully *et al*., 1986; Luborsky, 2002). This was further supported by similar mechanisms in other autoimmune pathologies, such as Graves' disease, where anti-thyroid-stimulating hormone receptor antibodies play an important role, or myasthenia, whose clinical signs are caused by anti-acetylcholine receptor antibodies.

In order to detect antigonadotrophin receptor antibodies, some authors investigated serum factors that might be able to inhibit the binding of gonadotrophins to their receptor, whereas others searched for factors capable of blocking the biological actions of gonadotrophins (Table V).

Inhibition of gonadotrophin receptor binding

Tang and Faiman (1983) investigated the binding capacity of gonadotrophins to their receptors by incubating radiolabelled FSH and LH with membrane extracts from bovine testes. They tested serum samples from nine patients with POF and showed that only one of them inhibited the binding of FSH to the testis extracts. They concluded that this patient had an anti-FSH receptor antibody. However, in a similar study, using radiolabelled hCG and corpus luteum extracts as source of receptors, none of 14 POF patients showed anti-LH/hCG receptor antibodies (Austin *et al*., 1979).

Chiauzzi *et al*. (1982) reported the presence of an FSH receptor-binding inhibiting factor in the serum of two patients with POF and associated myasthenia. They demonstrated the IgG isotype of this serum factor, showed its inhibiting effect to be dose dependent, and finally concluded that this antibody bound with a high affinity to the FSH receptor. They also showed a decreased synthesis of cAMP and androgen-binding protein (ABP) by *in vitro*-cultured rat seminiferous tubules, after adjunction of this antibody. Sera from other POF patients as well as from healthy controls did not yield any of these effects.

Moncayo *et al*. (1989) purified LH receptors from corpus luteum extracts by affinity chromatography and subsequently used them in an ELISA test. This allowed them to show the presence of antibodies against such semipurified LH receptors in 50% of patients with primary infertility and endometriosis, but also in 34% of IVF patients. However, in a recent study using the same technique these results could not be confirmed in POF patients (Wheatcroft *et al*., 1994).

Inhibition of biological activities

Various approaches have been used to detect antibodies that could inhibit the biological activity of FSH or LH, but unfortunately these studies are no more congruent than the former. Van Weissenbruch *et al*. (1991) cultured rat ovarian fragments in the presence of FSH and increasing concentrations of purified immunoglobulins from 26 POF patients. After the culture period, the tissues were sliced out and nuclear DNA was quantified by microdensitometry. The results showed that antibodies from >80% of the patients were able to inhibit FSH-induced DNA synthesis. On the contrary, none of the patients had antibodies that inhibited LH-induced testosterone synthesis in cultures of mouse Leydig cells.

Subsequently, the results of these studies using heterologous animal tissues have been questioned as it was shown that the binding of FSH to its receptor is highly species-specific (Tilly *et al*., 1992). Therefore Anasti *et al*. (1995) used transgenic cell lines expressing either the human FSH receptor or the human LH receptor. After incubation with serum samples from 38 POF patients, no inhibiting effect could be detected, either on FSH-induced progesterone synthesis, or on LH-induced cAMP production in these cell lines. In another study, granulosa-lutein cells were isolated in follicular aspirates from patients undergoing IVF and cultured *in vitro*. The progesterone synthesis of these cells could be inhibited by immunoglobulins from 20% of POF patients,

7% of poor responder IVF patients, and curiously from 85% of good responder patients, whereas none of the fertile control women showed these antibodies (Reznik *et al*., 1998). This observation has remained unexplained, but it allows us to question the pathophysiological role of antireceptor antibodies in ovarian failure.

Thus, it could be concluded that, in contrast with other autoimmune endocrine diseases, there is poor evidence for the involvement of anti-gonadotrophin receptor autoimmunity in human ovarian pathology.

Gonadotrophins as autoimmune targets?

Although blocking antibodies are usually considered to interact with receptors, as in the case of Graves' disease and myasthenia, the above-mentioned FSH or LH activity-inhibiting antibodies could also directly recognize gonadotrophins themselves. The existence of antigonadotrophin as well as antigonadotrophin receptor antibodies has been suggested in the context of resistant ovary syndrome (Platia *et al*., 1984).

Antibodies against the FSH β-subunit and some βFSH-derived peptides have been obtained by animal immunization. These antibodies are able to inhibit FSH activity *in vitro* (Westhoff *et al*., 1997), as well as *in vivo* (Ferro and Stimson, 1998).

However, few studies demonstrated the existence of antigonadotrophin antibodies in humans. Rabinowitz *et al*. (1979) reported the case of a patient with a complete βFSH deficiency and subsequent ovarian failure. In this patient, exogenous gonadotrophin treatment finally resulted in the appearance of anti-FSH antibodies. An immunization against exogenous gonadotrophins has also been suggested to explain the presence of anti-FSH and anti-LH antibodies in poor responder IVF patients (Meyer *et al*., 1990). In this study, 65% of poor responders had anti-LH antibodies, 92% of them had anti-FSH antibodies, whereas good responders had no antigonadotrophin antibodies. Later on, the same team searched for these antibodies in a group of 45 POF patients: only three of them had anti-LH antibodies, whereas none of them had anti-FSH antibodies (Luborsky *et al*., 1990).

Recently, our group investigated serum samples from 36 POF patients in a western blot approach with human ovarian extracts. Among the multiple bands obtained, a 15 kDa band was found in nearly all the samples. According to its size, this band could have represented βFSH, which was confirmed by the use of monoclonal anti-FSH antibodies. No anti-LH activity was detected by this technique in any of the samples. Subsequently, using a pep-scan technique, >100 overlapping βFSH-derived peptides were tested with the patients' antibodies. The recognized epitopes were distributed all along the βFSH molecule, but a region between the amino acids 78 and 93 was predominantly recognized in all samples, probably representing the immunodominant epitope (Gobert *et al*., 2001). As this part of the βFSH molecule is directly involved in receptor binding, the antibodies detected could readily explain the ovarian failure in patients who developed them.

Therefore antigonadotrophin autoimmunity may represent an interesting pathophysiological mechanism in POF, and will be further investigated.

The corpus luteum as an autoimmune target

Corpus luteum sections have frequently been used in immunofluorescence assays to detect SCA. In the presence of such antibodies, the immunostaining of paralutein cells appears to be a constant feature, whereas the staining of large luteal cells is more variable (Sotsiou *et al*., 1980). Corpus luteum tissue has also been used as a source of LH receptors (Moncayo *et al*., 1989) or to perform ELISA tests (Wheatcroft *et al*., 1994). Besides the steroidogenic enzymes recognized by SCA, no other autoantigen has so far been identified in the corpus luteum.

In bovine and human corpus luteum extracts, a potential 67 kDa antigen has recently been described that interacted with antibodies from 22% of patients with systemic lupus erythematosus (SLE). The presence of such antibodies in the patients who were all <40 years of age correlated with elevated serum FSH levels. Therefore, anticorpus luteum antibodies could represent the first stage of altered ovarian function in SLE patients (Pasoto *et al*., 1999), but the exact nature of the antigenic target is still unclear.

The zona pellucida as an autoimmune target

Numerous publications have dealt with a potential antizona pellucida (anti-ZP) autoimmunity in infertile patients. Older studies using indirect immunofluorescence on porcine oocytes generally reported a high prevalence of anti-ZP antibodies: between 15 and 68% of infertile patients were positive (Shivers and Dunbar, 1977; Mori *et al*., 1978).

Numerous other studies have investigated the significance of anti-ZP antibodies, but none of them could formally demonstrate a higher prevalence of these antibodies in infertile women (reviewed by Van Voorhis and Stovall, 1997). Since the late 1970s, the specificity of immunofluorescence reactions on porcine sections has been questioned, as there were positive reactions in up to 60% of healthy fertile women and even in 40% of men (Sacco and Moghissi, 1979).

In contrast with these studies using poorly specific methods, small patient groups, and few control subjects, more recent work using human zona pellucida has found a much lower prevalence of these anti-ZP antibodies. Thus Kamada *et al*. (1992) detected them in only 2.4% of 872 infertile patients. In IVF patients anti-ZP antibodies seem to be correlated with a lower fertilization rate (Mantzavinos *et al*., 1993; Papale *et al*., 1994). Nevertheless, the real significance of these antibodies remains to be established.

The oocyte as an autoimmune target

Anti-oocyte antibodies were first identified by Vallotton and Forbes (1966), and this was also one of the first descriptions of antiovarian autoimmunity. These authors used rabbit ovarian sections to detect antinuclear factors, because the large nuclei in the ovary made the identification of the fluorescence pattern quite easy. Surprisingly, the serum of a 53 year old woman who presented with pernicious anaemia and who had been menopausal since the age of 33 years induced a fluorescence of the oocyte cytoplasm. Subsequently, the authors found similar reactions with serum samples from 28 out of 187 patients presenting with various autoimmune diseases as well as in one out of 44 healthy blood donors. Among the 28 positive patients, nine had premature menopause (Vallotton and Forbes, 1966).

More recently, anti-oocyte cytoplasm antibodies were found in follicular fluids from IVF patients by immunohistochemistry on rat ovary sections. The prevalence of these antibodies was particularly high in cases of fertilization failure or oocyte retrieval failure (40 and 50% respectively). By contrast, only 3.7% of patients whose IVF was followed by an ongoing pregnancy had anti-oocyte cytoplasm antibodies (Horejsi *et al*., 2000).

However, very few studies using human oocytes have shown anti-oocyte antibodies in patients with autoimmune diseases, or other ovarian pathologies. Damewood *et al*. (1986) detected such antibodies by immunohistochemistry on human ovary sections in nine of 27 patients with POF. In their study, the cytoplasm of oocytes at all maturation stages was stained, even in primordial and primary follicles. Granulosa cells from preantral and antral follicles were also recognized by these antibodies. In another study, non-fertilized human oocytes from IVF patients were homogenized and used for an ELISA test, which detected anti-oocyte antibodies in 21 of 45 POF patients with or without associated autoimmune diseases (Luborsky *et al*., 1990).

The antigens recognized by anti-oocyte cytoplasm antibodies are still undetermined. Yet a potential immune target has been identified in post-thymectomy oophoritis, an experimental mouse model of autoimmune ovarian disease. The autoimmune oophoritis which develops in some strains of mice after neonatal thymectomy includes the appearance of anti-oocyte cytoplasm antibodies. Using an immunoblot approach, Tong and Nelson (1999) showed that these antibodies recognized a 125 kDa protein which they called OP1. Testing antibodies against a murine cDNA expression library allowed them to clone the OP1-coding sequence. Even if the exact function of OP1 is still not known, the presence of an ATP/GTP-binding site as well as phosphorylation sites on this protein suggests that it may be involved in some signal transduction pathway.

OP1 is exclusively expressed in the oocyte and persists in the early developing embryo up to the blastocyst stage (Tong and Nelson, 2000). In a knock-out model, inactivation of the *op1* gene results in sterility of female mice, because of an embryonic developmental arrest at the 2-cell stage, whereas folliculogenesis and fertilization are unaffected (Tong *et al*., 2000). Therefore *op1* represents a maternal effect gene, which plays an indispensable role in early embryonic development, probably by influencing activation of the embryonic genome. After this discovery OP1 has been called MATER ('Maternal Antigen That Embryos Require') (Nelson, 2001).

The human *MATER* gene has been identified very recently and shows ~67% of sequence homology with the mouse gene, which suggests that the MATER protein has similar functions in both species (Tong *et al*., 2002).

Thus the oocyte cytoplasm probably contains autoimmune targets that seem to be involved in ovarian disease as well as in the outcome of assisted reproduction techniques. However, their characterization remains difficult because human oocytes represent a very scarce material. MATER is a very promising candidate and, at present, important research work is underway to determine whether it could play a role in human ovarian autoimmunity, but also in repeated implantation failure after IVF or in embryonic developmental arrest.

Conclusion

A number of clinical and biological features indicate that autoimmunity is involved in several ovarian pathologies such as POF, idiopathic infertility, polycystic ovary disease, or endometriosis. The multiplicity of the above-mentioned potential autoimmune targets illustrates the variety of pathogenic mechanisms in ovarian disease, but their clinical significance and diagnostic relevance still give rise to controversy.

Yet further investigation of these ovarian targets may lead to: (i) the characterization of new molecules, such as MATER, that play an important role in reproductive physiology; (ii) a better understanding of the pathogenic mechanisms that may result in ovarian injury; (iii) the development of more accurate diagnostic tools in order to determine the real prevalence of autoimmune aetiology in ovarian disease.

The latter point is particularly important as a precocious and reliable diagnosis of an autoimmune aetiology is required to detect concomitant or future associated autoimmune disorders, as well as to select the patients in whom immune-modulating therapy may restore, at least temporarily, ovarian function and fertility.

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