Association of lower plasma estradiol levels and low expression of scavenger receptor class B, type I in infertile women

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Objective: To determine the expression of the scavenger receptor, class B, type I (SR-BI) in human granulosa cells.
Design: Prospective cohort analysis.
Setting: Tertiary academic university hospital.
Patient(s): Women undergoing IVF treatment.
Intervention(s): Granulosa cells were isolated from oocyte retrievals.
Main Outcome Measure(s): Total RNA and cell lysates were isolated from the granulosa cells, and SR-BI RNA and protein expression were quantified by real-time polymerase chain reaction and western blotting, respectively. Baseline and peak E_2 levels were drawn before IVF treatment and before hCG stimulation.
Result(s): The expression of SR-BI RNA and protein were positively correlated. The prevalence of low SR-BI RNA expression (defined as below 25th percentile) was 26%, whereas the prevalence of high SR-BI expression (defined as above 75th percentile) was 24%. Expression of SR-BI RNA was not correlated with body mass index, age, race or ethnicity, primary diagnosis of infertility, or pregnancy outcomes. However, baseline and peak E_2 levels were significantly lower in subjects with low SR-BI RNA expression as compared with subjects with high SR-BI expression ($P<.04$). There was a positive correlation between the number of retrieved ($P<.02$) and fertilized oocytes ($P<.002$) and SR-BI RNA levels.
Conclusion(s): Scavenger receptor–BI is expressed in human granulosa cells. Subjects with low SR-BI expression had lower baseline and peak E_2 levels and lower number of retrieved and fertilized oocytes. (Fertil Steril® 2006; 85:1391–7. ©2006 by American Society for Reproductive Medicine.)

Key Words: SR-BI, IVF, E_2, granulosa cells, HDL

It has been estimated that 15%–20% of all couples in America are infertile (1). Forty percent of this is attributed to female infertility; another 40% is caused by male infertility, whereas the remaining 20% is unexplained (2). In addition, fertility rates decline significantly as a woman ages. Heffner (3) reported that fertility rates for women younger than 30 years of age were more than 400 pregnancies per 1,000 exposed women per year, whereas women older than the age of 45 years had significantly lower rates, at 100 pregnancies per 1,000 exposed women per year. The lowered fertility rates in women of advancing years are associated with higher rates of spontaneous miscarriages, and many of these are caused by chromosomal abnormalities (3).

Investigators have studied the effect of the scavenger receptor class B, type I (SR-BI) on lipoprotein metabolism and fertility in SR-BI knockout (KO) mice (4–6). The SR-BI receptor was isolated and characterized as a high-density lipoprotein (HDL) receptor by Acton et al. (7). Scavenger receptor–BI participates in the selective uptake of cholesteryl esters from HDL (7) and low-density lipoprotein (8) and is regulated by corticotropin, estrogens, testosterone (T), cyclic AMP, gonadotropins, insulin, peroxisomal proliferator–activated receptor-α and -γ agonists, and polyunsaturated fatty acids (9–14). Scavenger receptor–BI is highly expressed in liver and steroidogenic tissue (adrenal and ovaries and testes) (15) and has been localized in atherosclerotic plaques and the endothelium (16, 17).

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Targeted mutations of the murine SR-BI receptor have demonstrated the importance of this receptor in fertility. Trigatti et al. (5) found that SR-BI KO males were fertile, whereas SR-BI KO females were not. There appeared to be no differences in gross ovarian morphology between SR-B1 KO and wild-type mice, but differences in lipid staining of the corpus luteum were apparent. Plasma progesterone (P) levels were not different and neither were estrus cycles or number of ovulated oocytes between female SR-BI KO and control mice (5).

Azhar et al. (18) has shown that selective cholesteryl ester uptake from HDL occurs in human granulosa cells, in a process likely dependent on SR-BI. Other investigators have shown that the follicular fluid of preovulatory follicles contains HDL (19). The purpose of this study was the following: [1] to determine SR-BI expression in human granulosa cells, [2] to assess the variability of SR-BI expression in a population of infertile women, and [3] to correlate SR-BI expression to clinical parameters related to infertility.

MATERIALS AND METHODS

Study Population

Between July 2004 and April 2005, granulosa cells were isolated from 68 women undergoing controlled ovarian hyperstimulation at The Johns Hopkins IVF Center, an urban academic tertiary hospital center. Women consented for IVF had their baseline E_2, FSH, and LH levels measured on cycle day 2 of a stimulation cycle. Women undergoing controlled ovarian hyperstimulation underwent pituitary suppression with either a GnRH agonist started in the luteal phase of the preceding cycle or a GnRH antagonist started by day 6 of the stimulation cycle.

Transvaginal ultrasound measurement of follicles and serum E_2 concentration measurements were performed as needed throughout the cycle to monitor follicular response to treatment. When at least three follicles reached a mean diameter of 18 mm, hCG was administered. Ultrasound-guided transvaginal oocyte aspiration was performed 34–36 hours after hCG administration.

Patients provided written consent for the IVF treatment; the protocol for use of granulosa cells as a byproduct of the oocyte retrieval was approved by The Johns Hopkins Institutional Review Board. Laboratory tests were performed as part of routine medical care and were analyzed in commercial laboratories. We did not have access to genomic material, nor were lipid profiles available for each subject.

Materials

We purchased the RNAlater, RETROscript, and PARIS kits from Ambion (Austin, TX). Scavenger receptor–BI and 18S primers and probes were custom designed by using Primer Express software and were purchased from Applied Biosystems (Foster City, CA). Human polyclonal SR-BI antibody was purchased from Novus Biologicals (Littleton, CO); human monoclonal GAPDH antibody, from Trevigen (Gaithersburg, MD); Percoll, from Sigma (St Louis, MO); human tubal fluid, from Sage BioPharma (Bedminster, NJ); Dulbecco's phosphate-buffered saline, from Gibco (Grand Island, NY); and ECL Chemiluminescent reagents, from Amersham Biosciences (Piscataway, NJ). All other reagents were chemical grade or better.

Granulosa Cell Retrieval and Isolation

Granulosa cells were recovered from follicular aspirates after removal of oocytes. Follicular aspirates from each patient were pooled, washed in human tubal fluid, and processed by centrifuge over 40% Percoll to remove red blood cells. Granulosa cells were washed again with Dulbecco's phosphate-buffered saline, and the cells were placed in RNA later. Of the total number of samples received, 50 were successfully processed for RNA and 42 for cell lysate, and 38 subjects had both RNA and protein measurements. The remainder was not used for the data analysis because the quality of the isolates was poor or there was an extremely low yield.

Expression of RNA

We extracted RNA from approximately 2.5×10^5 cells according to the PARIS Kit Protocol. After cell lysis and sample preparation, the RNA was obtained by column extraction as indicated in the protocol. Extracted RNAs were quantified spectrophotometrically and were stored at −80°C until reverse transcribed.

Reverse Transcriptase. Total RNA (1 μg) was reverse transcribed by using the RETROscript kit (Ambion), containing the random decamer primers, and moloney leukemia virus reverse transcriptase. Complementary DNA was synthesized at 55°C for 1 hour. Primers for human 18S and SR-BI were designed by using the Primer Express software. The primers and probes used for SR-BI (GenBank accession no. NM005505) and 18S (GenBank accession no. M10098) are shown in Table 1.

Quantification by Fluorescence Real-Time Polymerase Chain Reaction. The real-time polymerase chain reaction was conducted by using the ABI Prism 7900 HT Lightcycler by using the following program: 50°C for 2 minutes, initial denaturation for 10 minutes at 95°C, 40 cycles of denaturing for 15 seconds at 95°C, and annealing for 1 minute at 60°C. The reaction was performed by using 17 μL of Master Mix (10× buffer, $MgCl_2$, deoxyribonucleotide triphosphate mix; Amplitaq), 2 μL of primer mix (0.4 μM), 1 μL of probe (0.2 μM), and 10 ng of complementary DNA (SR-BI primers) to a 25 μL total reaction volume. To confirm accuracy of real-time polymerase chain reaction, the assay was run in triplicates for the target and the endogenous control. Expression of SR-BI mRNA was quantified by using the relative quantification method (ΔCt).

TABLE 1

Primers and probes used for SR-BI and 18S.

Gene	Primer sequence	Probe	Length (bp)
SR-BI		5′ ACA TCG TCA TGC CC 3′	94
Forward primer	5′ TTC CTC GAG TAC CGC ACC TT 3′		
Reverse primer	5′ GCA CCC AAG ACC AGG ATG TT 3′		
18S		5′ ACA TCG TCA TGC CC 3′	137
Forward primer	5′ CGG CTA CCA CAT CCA AGG A 3′		
Reverse primer	5′ TCG TTA AAG GAT TTA AAG TGG ACT CAT T 3′		

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Western Blot

Cells were lysed in cell lysis buffer containing 5% sodium dodecyl sulfate and 50 mM Tris. The supernatant was collected after centrifugation of the sonicated cellular lysate, and protein concentrations were determined by using the BCA Protein Assay Kit (Pierce, Rockford, IL). Ten micrograms of protein were separated by sodium dodecyl sulfate–polyacrylamide gel electrophoresis (10% Tris-glycine gels) and then transferred to polyvinylidene difluoride membranes. Nonspecific binding sites were blocked with 5% nonfat milk in Tris-buffered saline containing 0.1% Tween. Proteins were blotted by using human anti-rabbit SR-BI polyclonal antibody in a 1:250 dilution and human anti-goat GAPDH monoclonal antibody in a 1:1,000 dilution. Secondary anti-rabbit antibody was used in a 1:3,000 dilution and protein was visualized after treatment with ECL chemiluminescent reagents. Visualized bands were quantified densitometrically and normalized to GAPDH.

Statistical Analysis

Mean ± standard deviation (SD) were presented for continuous characteristics, whereas percentage distribution were reported for categorical variables. The relationship between SR-BI RNA expression and protein levels was graphically explored by using scatterplot, and the strength of association was examined by using Pearson's correlation. Mean difference in certain continuous clinical factors by predetermined level of SR-BI RNA expression also was examined by using Student's t test, with probability values of $<.05$ considered as statistically significant.

RESULTS

The characteristics of the study population are shown in Table 2. The mean age was 37.2 ± 4.0 years (range, 28–44 y),

TABLE 2

Characteristics of the study population.

Characteristic	Mean ± SD	Range
Age (y)	37.2 ± 4.0	28–44
BMI (kg/m^2)	25.2 ± 4.7	17.4–39.1
Baseline E_2 (pmol/L)	125.8 ± 46.9	73.4–286.3
Peak E_2 (pmol/L)	8,774.0 ± 5,086.5	1,858–24,801
Baseline LH (mIU/L)	3.7 ± 2.3	0.1–8.2
Baseline FSH (mIU/L)	5.7 ± 2.4	0.5–9.4

Note: BMI = body mass index; peak E_2 = maximum E_2 level obtained after hormonal stimulation.

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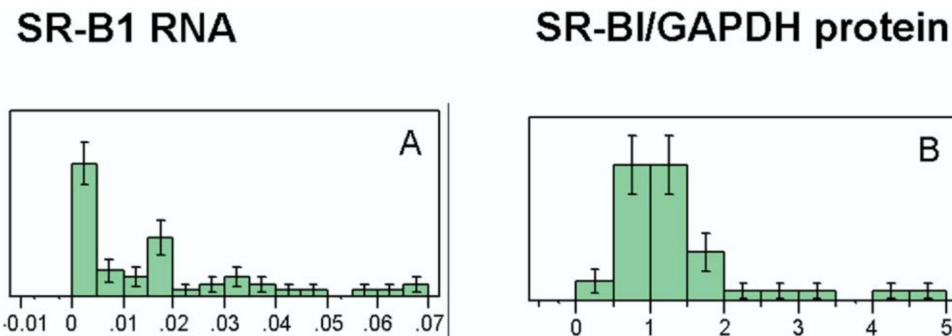
FIGURE 1

Distribution of SR-BI RNA (**A**) and protein (**B**) in the study population.



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with a mean body mass index (BMI) of 25.2 ± 4.7 (range, 17.4–39.1). The self-described racial distribution was Caucasian (75%), African American (17%), and Asian (8%). The primary diagnoses for infertility in decreasing order were endometriosis (22%), tubal obstruction (19%), male factor (15%), decreased ovarian reserve (15%), unexplained (7%), anovulation (7%), and other (15%).

As shown in Figure 1A, the mean SR-BI RNA level was 0.017 ± 0.02 ΔCt (median was 0.012). The ΔCt values corresponding to the 10th, 25th, 75th, and 90th percentiles were the following: 0.00078, 0.0017, 0.02950, and 0.048. As shown in Figure 1B, the mean SR-BI–GAPDH protein level was 1.24 ± 0.74 (median, 1.07). The protein values corresponding to the 10th, 25th, 75th, and 90th percentiles were the following: 0.531, 0.840, 1.40, and 2.09. There was a significant positive correlation between SR-BI RNA and protein levels from 38 subjects (r^2 = 0.11, $P<.04$; data not shown).

We then examined associations between SR-BI expression and clinical parameters such as age, BMI, race or ethnicity, primary diagnoses, baseline and peak E_2 levels, and pregnancy. There was not an association between SR-BI RNA expression and age (r^2 = 0.001, P=.82) or BMI (r^2 = 0.028, P=.27; data not shown). Neither was there an association between SR-BI RNA expression and race or ethnicity, primary diagnosis, or pregnancy outcomes (data not shown). However, the baseline E_2 level in women with low SR-BI RNA expression (defined as below the 25th percentile) was 49% lower (95.9 ± 24.0 pmol/L), compared with women with high SR-BI RNA levels (defined as above the 75th percentile; 188.7 ± 48.8 pmol/L; $P<.04$; Fig. 2). The peak E_2 levels (maximum level obtained after hormonal stimulation) also were significantly lower in women with low SR-BI expression (6,649.7 ± 1,030.1 pmol/L) as compared with in women with high SR-BI expression (1,1648.08 ± 2,456.3 pmol/L ($P<.04$; Fig. 3).

We also examined associations between SR-BI RNA levels and quality measurements, such as mean grade of embryos, and found no correlations (data not shown). However, as shown in Figure 4, there was a positive correlation between SR-BI RNA levels and the number of retrieved oocytes (Fig. 4A; $P<.02$) and the number of fertilized oocytes (Fig. 4B; $P<.002$).

DISCUSSION

The purpose of our study was the following: [1] to determine SR-BI expression in human granulosa cells, [2] to assess the variability of SR-BI expression in a population of infertile women, and [3] to correlate SR-BI expression to clinical parameters related to infertility. Cao et al. (15) had shown

FIGURE 2

Baseline plasma E_2 levels were lower in women with low SR-BI RNA expression (below the 25th percentile, *blue bar*) compared with in women with high SR-BI RNA expression (above the 75th percentile, *red bar*). The mean ± SE of plasma E_2 levels from women with low SR-BI RNA expression (n = 9) was 49% lower (95.9 ± 24.0 pmol/L) compared with women with high SR-BI RNA expression (n = 9, 188.7 ± 48.8 pmol/L, *$P<.04$).

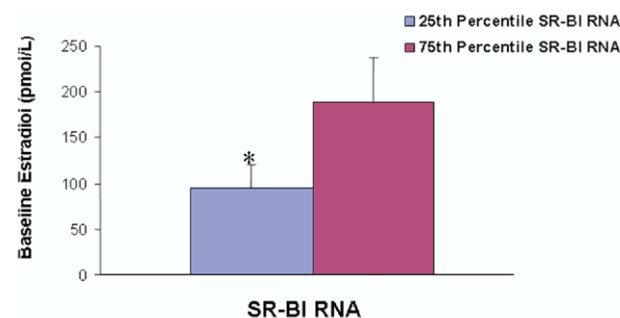

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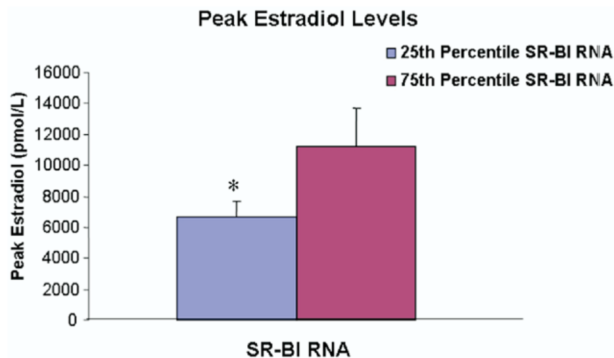
FIGURE 3

Peak plasma E_2 levels were lower in women with low SR-BI RNA expression (below the 25th percentile; *blue bar*) compared with in women with high SR-BI RNA expression (above the 75th percentile; *red bar*). The mean ± SE of plasma peak E_2 levels from women with low SR-BI RNA expression (n = 9) was 43% lower (6,649.7 ± 1,030.1 pmol/L) compared with women with high SR-BI RNA expression (n = 8, 11,648.1 ± 2,456.3 pmol/L, *$P<.04$).



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that SR-BI RNA was expressed in ovarian tissue (15), and we now show its expression in human granulosa cells.

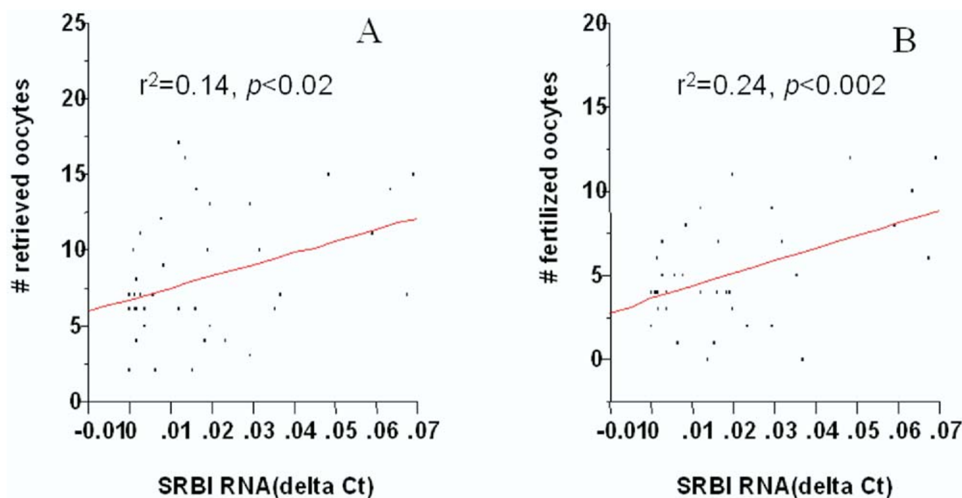
The prevalence of low SR-BI was approximately 26% of this selected population, whereas the prevalence of high SR-BI was approximately 24%. There have been few studies that have examined SR-BI expression in human tissues. Ramachandran et al. (20) had shown that SR-BI expression was increased in endometriosis biopsy tissue in women undergoing surgery for endometriosis.

Genetic studies have examined the association of different parameters (such as BMI and lipid levels) with single nucleotide polymorphisms (SNPs) or deletions within the SR-BI gene (21–24). Acton et al. (21) first reported associations of SR-BI SNPs with lipid levels and BMI. In a population of healthy individuals from Spain, women with an exon 8 variant had lower LDL cholesterol levels, whereas an intron 5 variant was associated with higher BMI compared with women with the normal allele (21). Hsu et al. (25) reported a deletion within the SR-BI promoter that decreased its activity and that presumably would have decreased SR-BI levels. Recently, Rodriguez-Esparragon et al. (26) showed that a mutant allele in intron 5 was associated with higher plasma levels of lipid hydroperoxides and lower SR-BI RNA expression from monocytes isolated from the study subjects. Their results suggested that this intronic SNP was a marker for diminished SR-BI expression.

We did not have access to genetic material from our study participants and therefore could not explore the possibility of alterations in the SR-BI locus. Nonetheless, we did not find associations between SR-BI RNA levels and age, BMI, race, or primary diagnosis of infertility. Future studies will address whether the prevalence of low or high SR-BI levels in women with infertility could be explained, in part, by variants in the SR-BI locus.

FIGURE 4

Positive correlation between SR-BI RNA levels and the number of retrieved and fertilized oocytes. The number of subjects matched for SR-BI RNA values and number of retrieved and fertilized oocytes was 38.



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Estrogen has been shown to regulate SR-BI expression in rodents (27, 28). Landschulz et al. (10) showed that rats that were fed high doses of estrogen had decreased hepatic SR-BI protein expression but increased SR-BI protein expression in adrenal tissue (10). Immunolocalization studies showed that SR-BI staining was substantially increased in the granulosa cells from estrogen-treated rats compared with control animals. Estrogen-treated rats also showed increased uptake of labeled lipid from HDL in adrenal and ovarian tissues, suggesting that estrogen increased SR-BI expression and function (10).

In our studies, we did find a significant association between lower baseline and peak E_2 and low SR-BI levels in this group of infertile women. Given that we did not find an association between SR-BI RNA expression and age, which suggested that an aging ovary with reduced E_2 production was not a likely explanation for lower SR-BI RNA levels, it is possible that reduced SR-BI expression (perhaps secondary to genetic variants) would lead to lower E_2 production from the granulosa cells. We did not find an association between low or high SR-BI expression and pregnancy outcomes. This might be attributable to the small size of our study population. Alternatively, significantly reduced pregnancy rates in human females may only be seen in women who are completely deficient in SR-BI, similar to what has been observed in SR-BI homozygotic KO female mice. Female heterozygotic SR-BI mice maintain normal fertility (6). We did, however, find a positive correlation between SR-BI RNA levels and the number of retrieved and fertilized oocytes, with the results showing lower numbers of retrieved and fertilized oocytes in subjects with lower SR-BI RNA levels. It is possible that for infertile women with low SR-BI expression, the difficulty might lie in the fertilization of the oocyte but not in the implantation of the blastocyst.

There are limitations in our study that merit discussion. First, the prevalence of low or high SR-BI expression was assessed in a population of healthy but infertile women. This limits our ability to extrapolate prevalence rates of SR-BI expression to the general female population. Second, we only were able to assess SR-BI expression in isolated granulosa cells; therefore, we are unable to determine whether changes in SR-BI expression were cell specific or generalized. Third, we did not have lipid values or genomic material to further characterize other aspects of SR-BI function. Fourth, the effects of GnRH antagonists or agonists on SR-BI expression are currently unknown. Fifth, our study was not significantly powered to determine correlations with SR-BI expression and pregnancy outcomes.

In summary, we have shown that human granulosa cells express SR-BI, that levels show biological variability, and that women with lower baseline and peak E_2 levels had lower levels of SR-BI expression and lower number of retrieved and fertilized oocytes. This suggests an important role of SR-BI in human ovarian function and its potential impact on female fertility.

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