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Minor Histocompatibility Antigens and the Maternal Immune Response to the Fetus During Pregnancy

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Abstract

The tolerance of the semiallogeneic fetus by the maternal immune system is an important area of research for understanding how the maternal and fetal systems interact during pregnancy to ensure a successful outcome. Several lines of research reveal that the maternal immune system can recognize and respond to fetal minor histocompatibility antigens during pregnancy. Reactions to these antigens arise because of allelic differences between the mother and fetus, and have been shown more broadly to play an important role in mediating transplantation outcomes. This review outlines the discovery of minor histocompatibility antigens and their importance in solid organ and hematopoietic stem cell transplantations, maternal T-cell responses to minor histocompatibility antigens during pregnancy, expression of minor histocompatibility antigens in the human placenta, and the potential involvement of minor histocompatibility antigens in the development and manifestation of pregnancy complications.

Keywords

Minor histocompatibility antigens; pregnancy; placenta

Introduction

Pregnancy provides researchers with a unique, naturally-occurring immunological model wherein the maternal immune system tolerates the semiallogeneic fetus. In human pregnancy, this tolerance is achieved both actively, via the expression of immuno-modulatory molecules on the surface of the placenta, and passively, through the restricted expression of classical MHC molecules on trophoblast cells[1]. Despite these adaptations, the maternal immune system is not naïve to the fetus. Rather, there is a robust and growing body of evidence indicating that, in both mice and humans, the maternal immune system actively responds to fetal antigens[2–6].

Immunogenicity of Minor Histocompatibility Antigens

Fetal antigens include both the major histocompatibility complex (MHC) and minor histocompatibility antigens (mHAgs)[3, 7]. MHC molecules are responsible for the presentation of foreign peptides to immune cells, and also are mediators of transplant

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rejection. Minor histocompatibility antigens are derived from functional proteins and can elicit an immune response due to allelic differences between individuals[7], typically single nucleotide polymorphisms (SNPs), insertions, deletions or presence of the antigen on the Y-chromosome (Tables I&II)[14,20–22,73–113].

In order for mHAgs to be recognized by T-cells, the antigens must be presented to T-cells in the context of specific MHC molecules, belonging to either Class I or II (Tables I&II)[14,20–22,73–113]. MHC Class II molecules bind to CD4+ T-cells and are primarily located on the surface of antigen presenting cells, most notably dendritic cells, macrophages and B cells. MHC Class I molecules bind to CD8+ T-cells and are present on the surface of most nucleated cells where they can present endogenous antigens and facilitate self vs. non-self discrimination by the immune system. MHC Class I is also critical for the process of cross-presentation whereby antigen presenting cells, typically dendritic cells, phagocytose exogenous material and process it for presentation on the MHC Class I molecule on the surface of the dendritic cell[8–10]. This allows for CD8+ T-cell recognition of antigens coming from tissues that do not express MHC Class I, including placental trophoblast[1]. Thus, placental debris containing fetal mHAgs could be released into the maternal blood stream, phagocytosed and processed by maternal dendritic cells and presented to maternal CD8+ T-cells, thus eliciting a maternal immune response to the fetus[11]. In addition to encountering and binding to the appropriate MHC for a specific peptide, responding T-cells must recognize the immunogenic peptide as foreign (i.e. non-self) and thus must come from an individual lacking the immunogenic peptide.

Histocompatibility Antigen 1 (HA1) is a widely studied mHAg that has been found on Hofbauer and trophoblast cells in the human placenta[12], and has been shown to be important for bone marrow transplantation outcomes[13]. The antigenic peptide that arises from HA1 results from a single nucleotide difference between the non-immunogenic peptide (KECVL**R**DDLLEA) and the immunogenic peptide (KECVL**H**DDLLEA)[14]. The immunogenic peptide can be presented in the context of at least four different Class I MHCs, including HLA-A*0201 (Table II)[14,20–22,84–113]. As a result of the immunogenic SNP, the binding affinity of the $HA1^{H}$ peptide to the HLA-A*0201 peptide binding groove on antigen presenting cells (APCs) is increased[15], thus leading to an immunogenic peptide that can be recognized by HLA-A*0201 restricted T-cells.

Recognition of the HA1 antigen can occur in the pathological situations of graft-versus-host disease and graft rejection, as well as in the physiological situation of pregnancy. In graft-versus-host disease, donor HLA-A*0201-restircted T-cells can recognize the immunogenic peptide in the antigen binding groove, thus eliciting an immune response targeting the recipients' tissues[13, 16]. Graft rejection occurs when recipient HLA-A*0201-restricted T-cells respond to and target the immunogenic peptide on the graft itself[17]. In the case of pregnancy, maternal HLA-A*0201 restricted T-cells can recognize fetal immunogenic HA1, as evidenced by the presence of HA1-specific T-cells in maternal blood following pregnancy[18]. The source of fetal HA1 could be either fetal cells that cross the placenta and enter the maternal blood stream and organs (microchimerism), or cells and vesicles released from the placenta. In each of the above situations, the T cells responding to the antigen are

both HLA-A*0201 restricted, and are derived from an individual lacking the immunogenic $HA1^H$ allele.

The probability of this interaction varies depending on the population frequency of both mHAg alleles and the MHC(s) restricting the immunogenic peptide. In the case of HA1, the population frequency of $HA1^H$ in a North American Caucasian population is approximately 44%[19] and the likelihood that an individual will possess one of the four MHCs capable of presenting $HA1^R$ (A*0201, A*0206, B*60 or B*40012)[14, 20–22] is at least 48.1%[23]. Consequently, the possibility that two individuals will be discordant for HA1 and that the individual with the non-immunogenic form of HA1 will have the correct MHC to present the immunogenic peptide is approximately 11.9%:

$$P(HA1^H) \times P(HA1^R) \times P(MHC) = 44\% \times 56\% \times 48.1\% = 11.9\%$$

Thus, histoincompatibility between individuals is far from a rare event: given the large number of mHAgs discovered so far, it is very likely that for a given pregnancy, there will be at least one if not many fetal mHAgs that could be recognized by the mother's immune system.

The Discovery of Minor Histocompatibility Antigens

The role of mHAgs in eliciting an immune response has been clearly demonstrated by transplantation studies. mHAgs were first discovered due to their role in modulating graft rejection and graft-versus-host disease in HLA-matched transplant recipients[13, 24, 25]. The first mHAg was discovered by Goulmy et. al. following the rejection of transplanted HLA-matched bone marrow cells from a male donor by a female recipient[25]. It was shown that cytotoxic T-lymphocytes (CTLs) isolated from the recipient's blood had the capacity to lyse HLA-matched male cells, indicating that the target was located on the Y-chromosome[26] and belonged to the HY family of mHAgs. Shortly after this discovery, the same group of investigators found that mHAgs could contribute to graft-versus-host disease, as donor CTLs can target and lyse recipient cells expressing a Y-chromosome-encoded antigen[24].

Since these original discoveries, fifty unique mHAgs derived from forty-three genes have been found (Tables I & II)[14,20–22,73–113]. These mHAgs arise from SNPs, presence on the Y-chromosome, deletions, insertions, frameshift mutations, nonsense mutations and splice variants. mHAgs are encoded on the Y-chromosome (Table I)[73–83] and on many autosomes (Table II)[14,20–22,84–113]. Expression of some mHAgs is restricted to hematopoietic cells or a select group of tissues, whereas other mHAgs are expressed ubiquitously. Given the numerous potential HLA combinations as well as the vast number of SNPs present in the population, it is likely that many more mHAgs exist that have not yet been identified.

One of the major constraints on research involving mHAg-specific CD8+ T-cells is their relative scarcity in both peripheral blood and at their target sites. Research using multimeric MHC reagents (MHC multimers) has estimated the prevalence of HY-specific T-cells in peripheral blood following multiple pregnancies with male babies at 0.0001% to 0.03% of the total CD8+ T-cell population[5]. MHC multimers are complexes comprised of 2–10 or more linked peptide-MHC ligands that can bind T-cells through the T cell receptor in an

antigen-specific manner[27, 28]. This allows for identification and quantification of T-cells specific for a particular antigen. However, in order to identify and characterize mHAg-specific T-cells, it is often necessary to expand the *ex vivo* population using cytokines and antigen, thus potentially altering the functionality of these cells both as a consequence of antigen/cytokine exposure and as a result of multimer-binding itself[29–31]. Therefore, caution should be used when assessing the functional significance of these cells *in vivo.*

Minor Histocompatibility Antigens and Transplantation Outcomes

Immune responses to mHAgs in the context of transplantation can have both beneficial and detrimental consequences for the patient. mHAgs appear to be the primary mediator of graft-versus-host disease in HLA-matched transplantations[13, 24–26], leading to the need for increased immunosuppression as well as other negative health outcomes including dermatitis, kidney failure and even death. However, mHAg specific donor T-cells can play an important role in mediating graft-versus-leukemia effects or graft-versus-tumor effects[32, 33]. These effects can significantly prolong the lives of patients who receive transplantations to treat various types of cancers and can help ensure longer periods of disease-free survival.

Recently researchers have proposed that modulation of T-cells specific for mHAgs may provide a unique opportunity for augmenting graft-versus-leukemia and graft-versus-tumor effects[34, 35], thus providing a potential avenue for increasing disease-free survival while subsequently reducing the need for immunosuppressive drugs. In this paradigm, donor T-cells specific for a particular mHAg whose expression is restricted to leukemic/tumor cells are isolated from the recipient's blood following the initial transplant and expanded ex vivo[34, 35]. These T-cells are then re-infused into the recipient following a disease relapse. A preliminary clinical trial targeting the mHAg HA1 showed some success in treating disease relapse, although a high percentage of the participants experienced serious side effects[35].

Minor Histocompatibility-Specific T-cells in Pregnancy

The role of mHAgs in pregnancy was first considered due to a finding by a number of researchers that parous female donors are more likely to elicit graft-versus-host disease in transplant recipients than non-parous or male donors[36–41]. These researchers hypothesized that this was due to the formation of mHAg-specific T-cells in the mother during or immediately following pregnancy.

Studies in mice have found that CD4+ and CD8+ T-cells can develop in response to the endogenous fetal antigen, HY[42]. Other mouse studies have demonstrated that the presentation of fetal antigens to maternal T-cells can begin as early as copulation and that paternal antigens can be found in the seminal fluid[11, 43]. In women, a number of studies have found T-cells specific for at least three mHAgs, HA1, HA2 and HY, following pregnancy[5, 18, 44]. These T-cells have been found up to twenty-two years following delivery of the baby, suggesting that at least a small cohort of these cells can persist for long periods of time[18]. It is thought that during normal pregnancy these cells are prevented from attacking the placenta and fetus via numerous tolerogenic mechanisms, thus allowing for a successful pregnancy. A disruption of this tolerance could have significant effects on clinical

outcome, as is evidenced by the links between mHAg expression, recognition by the maternal immune system and secondary recurrent miscarriage[45–47].

A recent study demonstrated that HY-specific CD8+ T-cells are elicited in maternal blood *during* human pregnancy with a male fetus[6]. These cells retained their proliferative capacity as well as their ability to lyse target cells and produce IFN-. The authors proposed that this indicates that fetus-specific T-cells are not completely deleted during pregnancy, as previously suggested[3, 48, 49]. As to why these T-cells do not cause the rejection of the fetus during normal pregnancies, there are at least three possibilities. The first is that the T-cells are incompletely activated during pregnancy, and thus lack effector function *in vivo*. The second hypothesis is that other cell types at the maternal-fetal interface, most notably regulatory CD4+ T-cells, prevent rejection of the fetus by promoting a tolerogenic environment as is indicated by the fact that regulatory T-cells are required for the success of allogeneic pregnancies in a mouse model[50, 51]. The third hypothesis is that the fetal-specific T-cells are unable to traffic to the maternal-fetal interface, and thus cannot mediate direct rejection of the fetus. This hypothesis is supported by recent work that showed an inability of maternal T-cells to traffic into the decidua during pregnancy as a result of epigenetic modifications leading to the loss of expression of specific chemokine genes by the decidual stromal cells[52]. Further to these mechanisms, the highly restricted expression of class I MHC molecules by placental trophoblast[1] most likely renders antigen-specific T-cells wholly or largely unable to target the placenta directly.

Minor Histocompatibility Antigens are Expressed in the Placenta

There are at least two likely sources of fetal mHAgs during pregnancy: the placenta and fetal cells trafficking from the fetus into the maternal blood supply (microchimerism)[53–56]. We have shown that at least six fetal mHAgs are expressed in human placental lysate, fetal cord blood and, most significantly, purified trophoblast cells. These findings provide strong evidence that the human placenta is one likely source of maternal immune exposure to fetal antigens during pregnancy (Table III)[12]. The close physical relationship between the syncytiotrophoblast, which covers the outer surface of the placenta, and the maternal blood supply, which surrounds the placenta, provides a likely avenue for maternal immune exposure to fetally-derived mHAgs[57, 58]. In addition to this close physical proximity, the syncytiotrophoblast undergoes a continual renewal process wherein the underlying cytotrophoblast fuses to give rise to the multinucleated syncytiotrophoblast and the excess, dead or damaged syncytiotrophoblast debris is released into the maternal blood space. This results in a large volume of fetally-derived placental debris being released into the maternal blood supply during pregnancy. In addition to the larger, shed debris, there is growing evidence that microvesicles/nanoparticles and exosomes are actively secreted from the surface of the placenta into the maternal blood space during pregnancy[59–61]. The total volume of this deported material has been estimated at 1g/day for the term placenta. Most of this placental material is easily cleared by the maternal system during normal pregnancy, but large, multinucleated syncytiotrophoblast debris has been found in the lungs of women who died of eclampsia[62–65]. Given the robust expression of fetal mHAgs in the syncytiotrophoblast and the large amount of syncytiotrophoblast debris that is released into

the maternal system, it seems highly likely that the placenta serves as a source of fetal antigens during pregnancy.

Clinical Implications

Of particular interest is the role that the mHAgs expressed in syncytiotrophoblast debris may play in the development or manifestation of numerous pregnancy complications. Recent work by our lab has shown that expression of at least one mHAg, HA1, is upregulated in preeclamptic placentas as compared to normotensive control placentas (Linscheid C and Petroff MG, unpublished data). We hypothesize that this increase in HA1 expression may contribute to disruption of the overall immunologic balance by increasing the antigenic load encountered by the maternal immune system in the context of increased proinflammatory cytokine release, a feature of preeclampsia and other pregnancy complications[66]. Specifically, the increased release of placental debris that is characteristic of preeclampsia[62–65, 67–69], compounded by the upregulation of HA1 expression in the deported syncytiotrophoblast, combined with an increase in inflammatory cytokines, most notably TNF-α and IL-6[66, 70], could alter the phenotype of both the dendritic cells that are presenting antigen to maternal T-cells as well as the T-cells themselves to promote anti-fetal immune responses, either during the current pregnancy or during subsequent pregnancies.

Dysfunction of the maternal immune system has been implicated in a number of other pregnancy complications, including secondary recurrent miscarriage. Epidemiologic evidence suggests that the recognition of fetal mHAgs may play an important role in secondary recurrent miscarriage, particularly if the preceding live birth was a male baby[45–47]. Specifically, Christiansen et. al. have found that women who experience secondary recurrent miscarriage are more likely than the general population to possess the appropriate Class II MHC to present Y-chromosome-encoded mHAgs and that secondary recurrent miscarriage is more likely to occur in women who have previously given birth to a male baby[45, 46], thus presenting the possibility that the development of secondary recurrent miscarriage is related to the generation of a maternal immune response specific for Y-chromosome-encoded antigens during the preceding, successful pregnancy. One theory regarding this phenomenon is that pregnancy complications late in the first pregnancy may disrupt the tolerogenic environment required for maintaining maternal immune tolerance towards the fetus and that this disruption contributes to the failure of subsequent pregnancies, especially those with a male fetus[71]. It is important to note that disruption of the tolerogenic environment and maternal T-cell recognition of both autosomal and Y-chromosome encoded fetal mHAgs may contribute to many cases of idiopathic infertility as well as numerous pregnancy complications.

A recent paper by Rowe et. al. (2012) found that in mice there is a substantial expansion of fetal-specific regulatory T-cells (T-regs) during primary and subsequent pregnancies[72]. The authors also found that resorption rates were significantly decreased in second pregnancies, due to a rapid expansion of a memory population of fetal-antigen specific T-regs that were formed during the first pregnancy. The authors propose that this mechanism may help explain why preeclampsia is more common in primiparous women as well as providing some insights as to why preeclampsia risk increases with interpregnancy interval. The role

of these fetus-specific T-regs in secondary recurrent miscarriage is unclear, but it seems possible that a failed expansion of fetal-specific T-regs during the first pregnancy or a loss of fetal-specific T-regs between the first and second pregnancies could contribute to the manifestation of secondary recurrent miscarriage.

Conclusions and Future Directions

Pregnancy presents numerous challenges to the maternal immune system, which must simultaneously tolerate the semiallogeneic fetus and protect both the mother and fetus from potentially life-threatening infections. The mechanisms by which this is achieved are varied and include the recognition of fetal antigens by maternal T-cells. There are a number of studies to suggest that this process has important implications for both maternal and fetal health. Developing a better understanding of the cellular interactions that mediate this tolerance may contribute to both the development of more successful transplantation protocols as well as the prevention and/or treatment of common pregnancy complications.

Future work should seek to determine the role of the maternal environment in modulating fetus-specific T-cell responses. Specifically, understanding how increased inflammatory cytokines and the production of reactive oxygen species, both of which occur in preeclampsia, affect mHAg-specific T-cell responses to placental and fetal tissues could provide important insights into the manifestation of the clinical symptoms of preeclampsia and other pro-inflammatory pregnancy complications. In addition, work designed to better understand the persistence and function of fetus-specific T-cells following parturition could provide important insights into the role of mHAg-specific T-cells in determining transplant success or failure. By better understanding the development and function of mHAg-specific T-cells during and following pregnancy, we can generate insights important for understanding immune tolerance in general and, more specifically, how maternal tolerance of the fetus is achieved during normal pregnancy and what happens when this tolerance is disrupted.

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Table I

Y-Chromosome Encoded Minor Histocompatibility Antigens

Minor Antigen	Gene	HLA	Peptide	Expression (mRNA)[1]	Ref.
A1/HY	DFFRY	A*0101	IVDCLTEMY	Ubiquitous	73
A2/HY	KDM5D	A*0201	FIDSYICQV	Ubiquitous	74
B52/HY	RPS4Y1	B*5201	TIRYPDPVI	Ubiquitous	75
B60/HY	UTY	B*60	RESEEESVSL	Ubiquitous	76
B7/HY	KDM5D	B*0702	SPSVDKARAEL	Ubiquitous	77
B8/HY	UTY	B*8	LPHNHTDL	Ubiquitous	78
TMSB4Y/A33	TMSB4Y	A*3303	EVLLRPGLHFR	Ubiquitous	79
$UTY_{139–147}$	UTY	A*2402	YYNAFHWAI	Ubiquitous	80
DQ5/HY	DDX3Y	DQB1*05	HIENFSDIDMGE	Ubiquitous	81
DRB1/HY	DDX3Y	DRB1*1501	SKGRYIPPHLR	Ubiquitous	82
DRB3/HY	RPS4Y1	DRB3*0301	VIKVNDTVQI	Ubiquitous	83

[1] Tissue expression information was obtained from biogps.org as well as the listed references.

Table II

Autosomally Encoded Minor Histocompatibility Antigens

Minor Antigen	Gene	HLA	Peptide[2]	Expression (mRNA)[1]	Ref.
ACC-1	BCL2A1	A*2402	DYLQ**Y**VLQI, DYLQ**C**VLQI	Restricted	20, 84, 85
ACC-2	BCL2A1	B*4403	KEFED**D**IINW	Restricted	20, 84, 85
ACC-4	Cathepsin H	A*3101	ATLPLLCA**R**	Restricted	86
ACC-5	Cathepsin H	A*3303	WATLPLLCA**R**	Restricted	86
ACC-6	HMSD	B*4402, B*4403	**MEIFIEVFSHF**	Restricted	87
CD19	CD19	A1*05, B1*02, DQ	WEGEPPC**L**P	Restricted	88
HA3	Lbc/AKAP13	A*0101	V**T**EPGTAQY	Ubiquitous	89
HA1	HMHA1	A*0201, A*0206, B*60, B*40012	VL**H**DDLLEA, KECVL**H**DDL	Restricted	14, 20–22
HA2	MYO1G	A*0201	YIGEVLVS**V**	Restricted	90–92
HA8	KIAA0020	A*0201	**R**TLDKVLEV	Ubiquitous	20, 93
HB-1	HMHB1	B*4402, B*4403	EEKRGSL**H**VW, EEKRGSL**Y**VW	Restricted	94–96
HEATR1	HEATR1	B*0801	ISKERA**E**AL	Ubiquitous	97
HER2_1170	HER2	A*0201	**G**CC	Restricted	98
LB-ADIR-1F	ADIR/TOR3A	A*0201	SVAPALAL**F**PA	Restricted	99
LB-APOBEC3B-1K	APOBEC3B	B*0702	**K**PQYHAEMCFL, **K**PQYHAEMCF, **K**PQYHAEMC	Restricted	100
LB-ARHGDIB-1R	ARHGDIB	B*0702	LPRACW**R**EA, LPRACW**R**EAR, LPRACW**R**EART	Restricted	100
LB-BCAT2-1R	BCAT2	B*0702	QP**R**RALLFVIL, QP**R**RALLFVI	Ubiquitous	100
LB-EBI3-1I	EBI3	B*0702	RPRARYY**I**QVA, RPRARYY**I**QV, RPRARYY**I**Q, AVRPRARYY**I**	Restricted	100
LB-ECGF1-1	ECGF1	B*0702	RP**H**AIRRPLAL	Restricted	101
LB-ERAP1-1R	ERAP1	B*0702	HP**R**QEQIALLA	Ubiquitous	100
LB-GEMIN4-1V	GEMIN4	B*0702	FPALRFVE**V**	Restricted	100

Minor Antigen	Gene	HLA	Peptide[2]	Expression (mRNA)[1]	Ref.
LB-NUP133-1R	NUP133	B*4001	SEDLILC**R**L	Restricted	102
LB-PDCD11-1F	PDCD11	B*0702	GPDSSKT**F**LCL, GPDSSKT**F**L	Ubiquitous	100
LB-PRCP-1D	PRCP	A*0201	FMWDVAE**D**LKA, FMWDVAE**D**L	Ubiquitous	100
LB-SON-1R	SON	B*4001	SETKQ**R**TVL	Restricted	102
LB-SSR1-1S	SSR1	A*0201	**S**LAVAQDLT	Restricted	100
LB-SWAP70-1Q	SWAP70	B*4001	MEQLE**Q**LEL	Restricted	102
LB-TRIP10-1EPC	TRIP10	B*4001	G**E**P**P**QDL**C**TL	Ubiquitous	102
LB-WNK1-1I	WNK1	A*0201	TLSPE**I**ITV	Ubiquitous	100
LRH-1	P2RX5	B*0702	TP*NQRQNVC*	Restricted	103–105
PANE1 (CTL-7A7)	CENPM	A*0301	*RVWDLPGVLK*	Restricted	106
SLC1A5	SLC1A5	B*4002	AE**A**TANGGLAL	Restricted	20, 107
SP110	SP110	A*0301	SLP**R**GTSTPK	Restricted	108
UGT2B17	UGT2B17	A*2902, B*4403	AELLNIPFLY	Ubiquitous	109, 110
UGTB17		A*0206	CVATMIFMI	Ubiquitous	107
UTA2-1	C12orf35	A*0201	QL**L**NSVLTL	Restricted	111
LAMA1	LAMA1	DRB1*0301	LLILRAIP**K**GIRDKGAK	Ubiquitous	112
LB-LY75-1K	LY75	DRB1*1301	GITYRN**K**SLM	Restricted	113
ZNF544	ZNF544	DRB1*0301	KQNSAFIN**D**EKNGADGK	Ubiquitous	112

[1] Tissue expression information was obtained from biogps.org as well as the listed references.

[2] Immunogenic amino acid differences are shown in bold and underlined. Peptides generated by alternative splicing are shown in bold. Peptides generated by a frameshift mutation are shown in italics. Peptides generated a translational termination codon are shown in italics and underlined. Peptides generated by a deletion are underlined.

Table III

Minor Histocompatibility Antigens Expressed in the Human Placenta

Minor Antigen	Gene	Function	Placental Expression[3]	Ref.
B52/HY	RPS4Y1	Ribosomal Protein S4	STB, EVTs, Macrophages, CTBs	12, 75
DRB3/HY	RPS4Y1	Ribosomal Protein S4	STB, EVTs, Macrophages, CTBs	12, 83
A2/HY	KDM5D	Protein containing zinc finger domains	Whole placental lysate, fetal cord blood, CTBs (mRNA only)	12, 74
B7/HY	KDM5D	Protein containing zinc finger domains	Whole placental lysate, fetal cord blood, CTBs (mRNA only)	12, 77
DQ5/HY	DDX3Y	RNA helicase, involved in spermatogenesis	Whole placental lysate, fetal cord blood, CTBs (mRNA only)	12, 81
DRB1/HY	DDX3Y	RNA helicase, involved in spermatogenesis	Whole placental lysate, fetal cord blood, CTBs (mRNA only)	12, 82
HA8	KIAA0020	Protein containing 6 PUF domains	STBs, EVT, CTBs	12, 20, 93
HA1	HMHA1	GTPase activating protein (GAP)	STB (first trimester only), EVTs, maternal and fetal leukocytes, macrophages, CTBs	12, 14, 20–22
ACC-1	BCL2A1	Anti-apoptotic factor	STB, EVTs, macrophages, CTBs	12, 84, 85
ACC-2	BCL2A1	Anti-apoptotic factor	STB, EVTs, macrophages, CTBs	12, 84, 85

[3]STB=syncytiotrophoblast, EVT=extravillous trophoblast, CTB=cytotrophoblast