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Endoplasmic Reticulum Aminopeptidase 2, a common immunological link to adverse pregnancy outcomes and cancer clearance?

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Abstract

Endoplasmic Reticulum Aminopeptidase 2 (ERAP2) trims HLA class I-binding peptides, determining the peptide repertoire presented for immune recognition. Variation in the ERAP2 amino acid sequence could affect the ability of some fetuses and tumors to achieve immune evasion. For example, homozygosity for an ERAP2 variant that has increased trimming efficiency for hydrophobic molecules has never been detected in mothers and fetuses. Thus, it is possible that this single nucleotide polymorphism (SNP) in the *ERAP2* gene has been selected against in order to prevent alteration of the immune privileged uterine environment, and to allow tumors to escape immune recognition. Currently, there are no immunological treatments or prophylactic approaches to ensure a healthy pregnancy outcome, and the success of cancer immunotherapies is variable. Understanding the role of ERAP2 in immune evasion mechanisms in pregnancy and cancer may improve fetal survival and tumor clearance. This review summarizes current knowledge about ERAP2 and its N392 variant, and their relationship to pregnancy outcomes and cancer immune evasion/recognition.

Keywords

ERAP2; Pregnancy; Cancer; Immune Evasion; Immune Surveillance

Introduction

Immune evasion is good for fetal and tumor growth. Immune detection, on the other hand, is bad for both the fetus and tumors. Evidence is accumulating to support the pivotal role of ERAP2 in immune evasion mechanisms. A better understanding of its role in immune evasion or recognition may allow the development of prophylactic and therapeutic

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Conflict of interest

There is no conflict of interest.

treatments for fetal rejection and tumor clearance. This review will address three main objectives; 1) to introduce genetic studies that suggest how the N392 ERAP2 variant is selected against in populations for potential detrimental effects on pregnancy; 2) to provide an overview of ERAP2 in pregnancy and cancer, and their roles in immune evasion; and 3) to document the need to explore how N392 ERAP2 may be involved in fetal rejection, and how this knowledge can be applied to tumor clearance.

ERAP

Endoplasmic Reticulum Aminopeptidase (ERAP)1 and ERAP2 are zinc-metallopeptidases of the oxytocinase M1 subfamily, which share consensus zinc-binding motifs essential for their enzymatic activity. Most of the antigenic protein degradation occurs in cytosolic proteasome complexes [1]. However, when additional processing of peptides is necessary to increase and to refine the variety available for binding to Major Histocompatibility Complex (MHC), also known as Human Leukocyte Antigen (HLA) class I molecules, the peptides are transported to the endoplasmic reticulum (ER) by a transporter associated with antigen processing protein (TAP) [2–4]. ERAP enzymes then trim amino acid residues from the NH2 terminus of polypeptides to generate the optimal length antigenic peptides for loading onto HLA class I molecules [5, 6].

The human *ERAP1* and *ERAP2* genes are located on chromosome 5q15 in the opposite orientation. Human *ERAP2* has no orthologues in rodents, and evolutionary studies suggest that *ERAP2* originates from a relatively recent duplication of the *ERAP1* gene [7]. It is not known exactly when the *ERAP* gene evolved, and equally uncertain is the functional consequence its evolution has for human pregnancy and cancer immunology. However, ERAP2 protein expression is detected in many tissues, and is induced by type I and type II interferon (IFNs) and tumor necrosis factor-alpha (TNF-α), suggesting that ERAP2 is essential for immune control, and that further investigation is needed to clarify its roles [8, 9].

ERAP2 and Pregnancy

A genome-wide association study (GWAS) suggested a role of the *ERAP2* locus in preeclampsia (PE) [10]. PE affects 3–8% of pregnancies worldwide, with the highest (10%) among African Americans. It leads to potentially devastating complications for both the mother and fetus [10–12]. Johnson *et al.* were the first investigators to report that the *ERAP2* gene was associated with PE in Australian and Norwegian populations [10]. Recently, our group reported the fetal *ERAP2* SNP rs2549782 genotype is associated with a higher risk for PE in African American women (P=0.009) [13]. These findings are supported by a recent study, which revealed elevated levels of ERAP2 transcripts in the decidua of PE patients, which contradicts earlier observations of expression of this gene being down-regulated in first trimester placentas of women who subsequently developed PE [14–16]. One potential explanation for the different observations relates to when and which ERAP2 variant transcripts are expressed and translated to affect the maternal immune response. PE is first diagnosed around 20 weeks of gestation, but it is thought that the problem arises as early as during placentation. The determination of aberrant gene expression prior to development of maternal symptoms suggests ERAP2 is involved in the early disease course.

ERAP2 is a good candidate to contribute to the development of PE and other pregnancy related diseases because of its involvement in the regulation of the immune response, pro-inflammatory cytokine production, and blood pressure [5, 17–20]. PE is associated with predominant presence of T Helper Cell Type 1 (Th1), and is considered to be a failure of immune tolerance resulting in poor placentation, exacerbated inflammation, and endothelial dysfunction [21]. Thus, it is critical to determine how and when paternal antigen presentation on HLA is altered by ERAP2 variants, and its subsequent immune modulation that could determine the pregnancy outcomes.

The following observations provide evidence for racial differences in the role of ERAP2 in risk for PE association. In most populations, the major T allele of rs2549782 (gain-of-function) haplotype structure of ERAP2 N392 pairs with the G allele of rs2248374 which causes nonsense-mediated RNA decay (loss-of-function), such that the N392 ERAP2 isoform would never be expressed [10]. However, the strong linkage disequilibrium described above and ERAP2/PE association was not detected in a Chilean population, suggesting that N392 ERAP2 could be detected. However, we found that homozygosity for the T/T N392 ERAP2 (“gain-of-function”) allele is never detected in the mother or fetus in normal pregnancies in the Chilean population studied (n=528 dyads) [22]. One hypothesis to explain these observations is that “hyper” trimming capability for hydrophobic peptides alters the peptide and HLA class I repertoire in cells triggering immune activation, creating a non-permissive uterine environment for trophoblast cell/fetal survival [23].

ERAP2 and Reproductive/Cancer Immunology

Interest in the immunology of pregnancy was inspired by the realization that expression of paternal histocompatibility antigens by the fetus and placenta should provoke a tissue rejection response similar to that observed following organ transplantation [24]. ERAP2 link to the immune system derives from its ability to trim HLA class I-binding antigens, determining the peptide repertoire presented for T cell recognition [8, 19, 25–27]. The concerted effort of ERAP1 and ERAP2 determines the efficiency of peptide editing [26]. However, as it is mentioned above a single nucleotide polymorphism (SNP) rs2549782 in ERAP2 results in an amino acid change of Lysine (K392) to Asparagine (N392-isoform) that increases ERAP2 protein interaction with hydrophobic peptides by 165-fold, altering the peptide and HLA class I repertoire in cells [23]. We hypothesize that this ERAP2 variant could either generate or destroy immunodominant epitopes to modulate immune recognition.

On the other hand, ERAP2 deficiency can contribute to immune evasion by tumor cells in vivo [7, 15]. Loss of the ERAP2 protein has been observed in renal carcinoma, colon adenocarcinoma, melanoma, and ovarian cancer, suggesting that the lack of ERAP2 benefits cancer growth and/or maintenance [15]. Cancer cells can avoid inducing an immune response by any combination of these steps: 1) inhibiting tumor antigen transport to endoplasmic reticulum (ER), 2) improper trimming of peptides in the ER and/or 3) inadequate peptide presentation on HLA molecule. Currently, there is evidence that disruptions in antigen transportation and antigen presentation are used in immune evasion [28, 29]. However, the role of ERAP2 in immune evasion has yet to be fully elucidated. The

first observation of the low expression level of ERAP2, ERAP1 and HLA class I was made in the most aggressive form of neuroblastoma [9].

Previously, researchers have demonstrated that ERAP1-mediated trimming is necessary for the generation of many antigenic epitopes but can also lead to destruction by trimming them too small for HLA binding [27]. Based on this observation, Stratikos and colleagues attempted to develop a potent ERAP1 inhibitor using a structure-guided design approach, focusing on the Zn-containing active enzyme site. They demonstrated that one of the inhibitors, DG013A, enhances antigen presentation by HeLa cells and elicits a potent Cytotoxic T Lymphocyte (CTL) response against murine colon carcinoma cells [30]. In this mouse model, inhibition of ERAP1 was an effective way to improve immunodominant epitope process, presentation, and CTL response. However, this model does not address if the response will be the same if ERAP2 was present and inhibited. Any aberrant generation of antigenic peptides and alteration of MHC repertoire can lead to either immune evasion or activation. Thus, we need to better understand the role of ERAP2 in either to inhibit or enhance its action to develop more effective cancer treatments. Unfortunately, determining ERAP2's role in cancer targeting and cell clearance has been confounded because animal models lack ERAP2 orthologues.

The fine balance of epitope destruction/generation by ERAP1 and ERAP2 is necessary for healthy fetal and cancer cells. On the contrary, if we understand how those peptide-processing functions are affected by these enzymatic activities, the fetal rejection can be prevented and tumor clearance can be promoted. Especially, by attempting to understand the evolutionary selection against N392 ERAP2 and its mechanism of action in the immune system, we might obtain new insight into ERAP2's role in immune recognition in both reproductive and cancer immunology.

HLA-C association in Pregnancy and Cancer

Decidual natural killer (dNK) cells are the most abundant lymphocytes (70%) during early gestation [31, 32] and are virtually absent by the end of pregnancy [31, 33, 34]. These NK cells are phenotypically and functionally different from the systemic circulating NK cells [35]. Several studies suggest that the primary role of dNK cells is to encourage those changes in uterine vasculature necessary for efficient maternal blood flow through the placenta permitting nutrient and gas exchange. The failure to establish a proper vasculature results in placental hypo-perfusion which is believed to trigger complications such as PE, intrauterine growth restriction, unexplained stillbirth, recurrent miscarriage, or preterm birth [36].

The recent work of Hiby et al. showed that placentation is regulated by the interactions between maternal killer immunoglobulin-like receptors (KIRs) on dNK cells and HLA-C molecules on invading fetal trophoblast cells [37]. The trophoblast cells that invade the uterus have a unique pattern of HLA class I expression consisting of invariant HLA-G, HLA-E and the polymorphic HLA-C, and no expression of highly polymorphic HLA-A or HLA-B [38]. Therefore, only HLA-C presents polymorphic forms necessary for the recognition of fetal alloantigens. Due to high variability and genetic diversity of KIR in

different populations, certain combinations of maternal KIRs and fetal HLA-C ligands could determine the success or failure of a pregnancy.

There are 2 basic KIR haplotypes, A and B. The only difference between the two is that haplotype B has additional activating receptors. Similarly, HLA-C ligands for KIRs are divided into 2 groups. Group 1 HLA-C (C1) allotypes bind inhibitory KIR, while group 2 HLA-C (C2) allotype binds both inhibitory and activating KIRs on uNK cells. Specifically, this study concluded that the maternal activating *KIR AA* frequencies are increased in affected pregnancies only when the fetus has more *HLA-C2* gene expression than the mother [37]. Furthermore, Hackmon et al. confirmed the distinct expression of HLA-F, HLA-G, HLA-E, and HLA-C in placental tissue, especially on extravillous trophblast cells (EVT). This study provided the first evidence of increased HLA-C expression in parturition that may indicate modulation of the immune-inflammatory role of HLA-C [39]. These combined studies raise the possibility of the deleterious allogeneic effect stemming from paternal HLA-C, specifically C2 group. Altogether, the missing piece of the puzzle is the functional mechanism to explain the pregnancy outcomes determined by the KIR/HLA-C interactions due to hyper trimming effect of paternal antigens by N392 ERAP2 and how this translates into different uNK cell functions, which is illustrated in Figure 1. Trophoblast cells expressing the N392 ERAP2 isoform, which alters class I antigen expression, may now become target cells triggering NK cell-mediated lysis, and thus results in fetal “rejection,” and may explain why this particular genotype is never detected in populations studied to date.

Furthermore, it is not surprising that trophobast cells only express HLA-C to be protected from the maternal immune system. Similarly, HLA-C has been shown to be associated with protection of nasopharygeal carcinoma and cervical neoplasia, as well from the host immune system [40]. Nature possibly meant HLA-Cs main role to be protective, but the evidence of biological function supporting HLA-C-restriced CTL responses suggests that when this tolerance is dfisrupted by an intrinsic factor such as a ERAP2 SNP (gain-of-function), the host immune response could be detrimental to fetal and tumorigenic cells.

The main question is if HLA-C restricted allogeneic paternal or tumorigenic antigens are generated by ERAP2 to induce T and NK cell response. This is becoming a feasible hypothesis since the biological significance of HLA-C restricted responses was confirmed as the HLA-C antigen restricted alloreactivity CTL response was established particularly in chronic infection of Epstein-Barr virus ad HIV infections [41, 42]. To date, the HLA-C alleles have been involved in several human diseases, emphasizing its critical role, but it is not clear if the relationship is the result of HLA-C function as a T-cell restricted response, or as a consequence of its interaction with KIRs on NK cells.

Conclusion

Fetal and tumor growth have many similarities such as cellular invasion, angiogenesis, rapid growth, and immune modulation [43]. In this review, we have briefly summarized additional similarities based on recent knowledge of the involvement of ERAP2 in immune recognition. Genetic evidence provided by the association of the ERAP2 variant with a

pregnancy related disorder (PE), and the fact that this variant is evidently selected against to protect the uterine environment warrants further investigation. Conversely, this knowledge could be used to develop targeted immunotherapies for cancer. If N392 ERAP2 expression is 100 percent successful in preventing full term fetal development, resulting in zero detection, what if N392 ERAP2 is introduced into tumors? Could it promote efficient immune clearance of tumor cells?

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Highlights

- Current knowledge of Endoplasmic Reticulum Aminopeptidase 2 (ERAP2) in pregnancy and cancer is presented.
- In some cancers, lack of ERAP2 expression may benefit tumor immune evasion.
- In pregnancy, hyper trimming of an ERAP2 variant may cause fetal rejection.
- Speculation on how knowledge of ERAP2 function in pregnancy can be translated into translational tumor clearance.

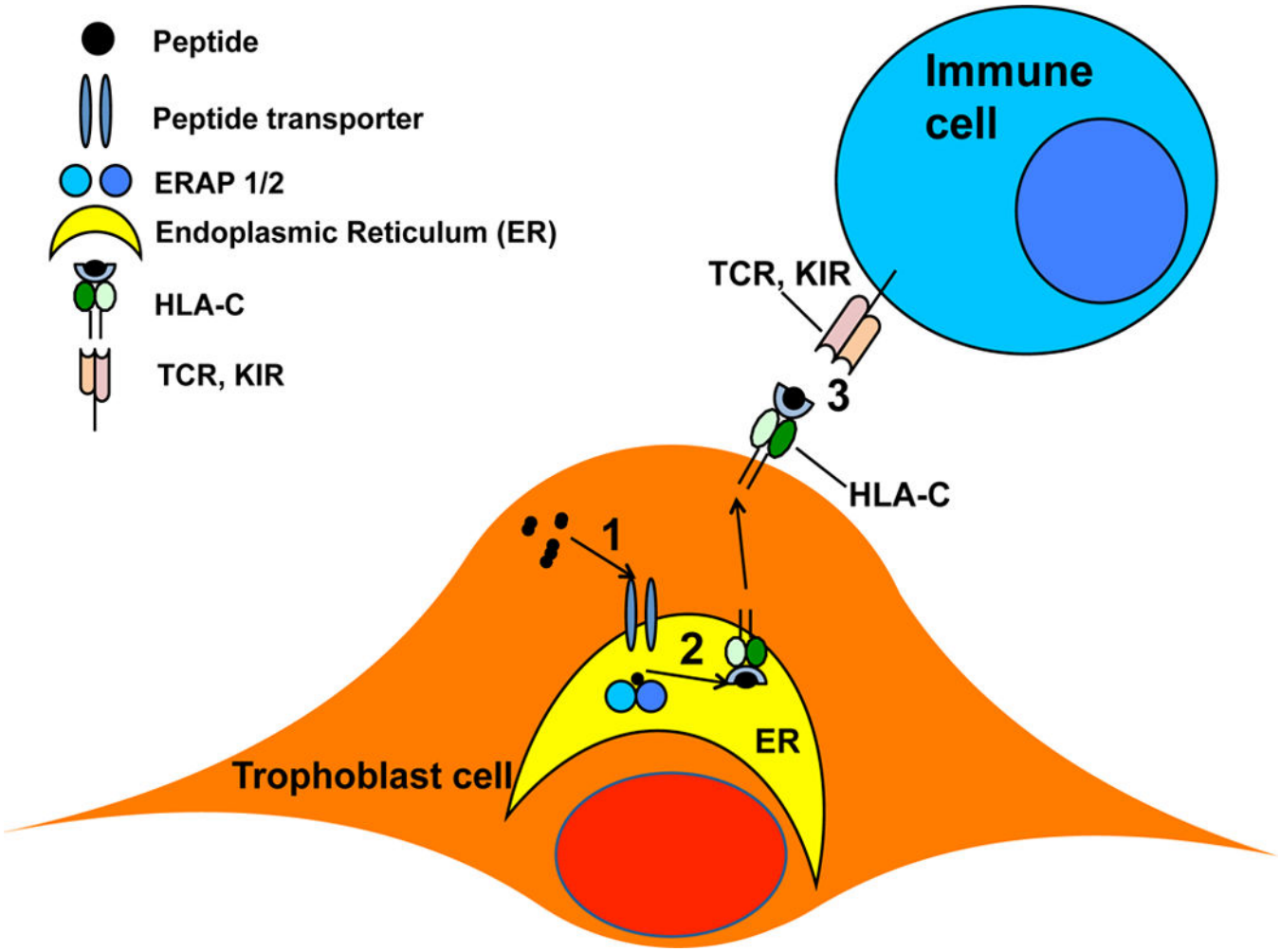

Figure 1.
Illustration of peptide 1. transport, 2. process, and 3. presentation by trophoblast.