A Review On Nk[46] the Immunogenetic Predictive Candidate Gene of Unexpplained Recurrent Miscarrages

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Abstract

Recurrent miscarriages of unknown etiology present a challenge to the clinician with a profound socio-psychological impact in addition to pathophysiological burden for affected couples. Currently, there exists a plethora of articles dealing with genetic polymorphisms associated with recurrent miscarriages with the polymorphic analysis being concentrated on a limited numbers of genes. The NKP[46] gene a major regulator of natural killer cell function has a strong biological literature which suggests a putative role in the immunogenetics of unexplained recurrent miscarriages. Therefore plausible to propose the NKp[46] gene a candidate gene in the etiology of unexplained recurrent miscarriages.

Keywords: NK Cells; NKP[46]; Genes; Immunogenetics;

Introduction

In humans pregnancy may be interrupted at various stages of development. Receptive interruptions of pregnancy resulting in loss are referred to as Recurrent Miscarriages. Miscarriage is defined by the World Health Organization as a loss of a viable pregnancy before 24 weeks of gestation [1]. Miscarriages remain the most common pregnancy complications [1]. The exact frequency of miscarriages is, however unknown as miscarriages frequently occur before the woman is aware of her pregnancy. It is estimated that more pregnancies are lost spontaneously than actually carried to term [2,3]. Suggested risk factors for recurrent miscarriages include: Genetics, immunologic, anatomic, endocrinilogical and environmental factors [3]. However, in about 50% of cases, the etiology is unknown. Since a proportion of recurrent miscarriages are thought to be immunologic and genetic origin, investigations of genes involved in biological mechanisms within the feto-maternal interface becomes suggestive [2]. Sequence variations have been located in genes involved in immunologic mechanisms.

The CTL-A gene is a regulator of T-cell activation and an A/G polymorphism in exon 1 of this gene has been reported to be associated with recurrent miscarriages in the Chinese population [3]. Polymorphisms in the HLA –G promoter region, the HLA-G *0104 and *0105 alleles and the HLA-DRBI *1505 allele have been equally associated with the immunopathogenesis of recurrent miscarriages but polymorphisms has not yet been studied extensively on many other genes including the NKP[46] gene [4-6]. Studies have also shown higher levels of nucleotide polymorphisms in many other populations [7]. Currently, research is focused on cellular constituents or processes to explain the pathophysiologic mechanisms underlying recurrent miscarriages [7]. Natural killer cells have been extensively evaluated as probable contributory factors [8]. They are the predominant leucocytes populations present in the endometrium during the period of implantations and early pregnancy, functioning as local immunomodulators in the regulation of trophoblast and placental growth [8]. Being the predorminant leucocytes present in implantation sites during the first trimester. , a role for this particular interaction regarding materno-fetal tolerance is suggestive in recurrent miscarriages , the fetus being semi allogenic in nature [9,10]. Previous studies have reported that reduction in the number of peripheral natural killer cells enhances the progression of normal pregnancy and that an increased natural killer cell populations is associated with miscarriages [8]. Polymorphisms in some natural killer cell regulatory genes as a result may be an unexplainable factor underlying recurrent miscarriages in some individuals. The genetic origin of disease either partly or wholly due to abnormalities within the genetic code. Genetic polymorphisms are variations in DNA that are observed in 1% or more of the population [11]. Most common polymorphisms are potential regulatory polymorphism located in noncoding regions and may have np discernable effect on the protein products [11,12]. However, some polymorphisms may alter protein structure and function through a single nucleotide base substitution in a gene's coding region and may increase or decrease gene expression either by affecting mRNA stability [11]. Such polymorphism could as a result present apathophysiological conditions. The

study of genetic polymorphisms helps define pathophysiologic mechanisms, identify individuals at risk for disease and suggest novel targets requiring only access to a polymerase chain reaction machine, funding for reagents and DNA and samples from cases and controls [11,12].

NK Cells

Natural killer cells are the most recently describes of the innate immunocompetent cells. There is vivid increase in the number of these cells during the secretory phase of the menstrual cycle as progesterone levels increase. These numbers rise further if the pregnancy ensues. Since progesterone levels drop at the end of the menstrual cycle and NK cells also undergo death, it has been proposed that their survival depends on progesterone level [13]. NK cells become granulated and come in contact with vessels and endometrial glands [13]. They are largely granular lymphocytes that populate the materno- foetal interface during pregnancy, protecting the mother and foetus. The materno-foetal interface during pregnancy represents an immunological battle-field characterized by direct contact between foetal antigens and maternal immunocompetent cells from the uterus, the foetus being semi allogenic in nature. Therefore, for successful pregnancy to occur the immune response by immunocompetent cells such as NK cells is modulated at the materno-foetal interface throughout gestation and recurrent miscarriages maybe a result of a failure of such modulations in some individuals. Phenotypically, natural killers cells are characterized by the expression of CD56 and CD16 receptors on their cells surface. Based on the concentration of CD56 antigen, they can be divided into two subpopulations, CD56dim, and CD56 bright. CD56dim cells demonstrate high toxicity invitro whereas CD56 bright cellsexhibit low cytotoxic capacity; however the CD56bright produces important immunoregulatoy cytokines particularly interferon gamma (IFN-Y). Approximately 90% of peripheral natural killer cells are CD56dim and express high level of CD16 while the remaining 10% are CD56bright with minimal or no expression of CD16. Several studies have demonstrated that peripheral natural killer cells do not change during menstrual cycle; however numerical and functional decrease has been observed during pregnancy suggesting the failure of their regulation as a major factor in recurrent miscarriages [14]. The human endometrium contains a substantial population of natural killer cells referred to as uterine natural killer cells (uNkcells). Atlthough there is no concensus about the origin of uterine natural killer cells, it is believed that mature peripheral natural killer cells or immature precursors may migrate into the endometrium from the blood possibly in response to chemokines produced by cells within the endometrium. The production of CXCL-12 by extravillous trophoblast (EVT) cells has been linked to be able to attract natural killer cells into the individual in pregnancy while transforming growth factor beta 1(TGF-BETA 1) has equally been implicated to modify peripheral blood natural killer cells to uterine natural killer cells. Studies have shown that endometrial natural killer cells participate in the materno-foetal interactions during implantation, trophoblast invasion, placentation, organogenesis and foetal development which represent a new perspective in the field of reproductive

immunology [14]. The prevalence of NK cells in women with RM is unclear. A recent study had concluded that women with recurrent miscarriages had a significantly higher NK percentage than controls [15].

NKp[46] Gene

The NKp[46] gene (NCRI, CD335) is a member of natural cytotoxicity receptors; activating receptors capable of inducing natural killer cell mediated cytotoxicity. It is stably expressed and specifically present on all resting and activated human natural killer cells [16]. NKp[46] is a 46KDa type-1 transmembrane glycoprotein that is not only a member of the natural cytotoxic receptors (NCRs) family but also a member of the immunoglobulin superfamily [16]. It is a 9 exon count protein encoded by the NCR1 gene located on the human chromosome close to the highly polymorphic Leucocyte Receptor Complex. NKp[46] gene is currently considered the most reliable identifying marker for natural for natural killer cells across species [16]. Natural Killer cells are effector regulatory lymphocytes of the innate immune system that contribute to tumor surveillance hematopoietic allograft rejection, control of microbial infections and pregnancy [17]. They have also been suggested to provide a link between innate and acquired immunity through production of cytokines and interaction with antigen –presenting cells [17]. Since the NKp[46] gene is thought to be the main natural killer cell activating receptor and also proven to display functional cross talk with other natural cytotoxic receptors and natural killer cell activating receptors, we propose a strong involvement of this gene in the pathogenesis of unexplained recurrent miscarries suggesting it a candidate gene for the condition [18].

The Candidate Gene Approach

The candidate gene is a gene of documented biological activity involved in the pathophysiology or biological pathways of a given medical condition with polymorphic activity. This condition is a major factor of inter-individual variability [19]. New effective methods for genetic screening together with the information offered by the Human Genome project have made the candidate gene approach a commonly used method to search for disease genes as information on physical locations and sequence arrangement of many genes are available. The candidate gene approach can be applied when the biochemical or physiological background of the defect of interest is known, when a chromosomal region has been linked to a disease or if an animal model of a disease has established [20,21]. Interaction partners of identified proteins defective on a disease could as well be considered as a candidate gene for disease of interest. The mouse is widely used model organisms for studying mammalian gene functions and genes causing a phenotype in a mouse can be used as a candidate gene in human disease studies. The NKp[46] gene has been extensively studied in the mouse and proven to excite same qualities in human. This is however speculative.

Conclusion

Progress in natural killer cell receptor genetics may likely prove their significance in pathological conditions such as

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recurrent miscarriages. We propose a genome wide association study of theNKP[46] gene as a predictive candidate gene in the etiology of unexplained recurrent miscarriages. It is however, the unlimited potentials of genetics to help predict who will get a disease and /or who once diagnosed with a disease will have an unfavorable prognosis that inspired review.

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