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Natural Killer Cell

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1. Introduction

NK cells protect against a variety of cancers and infection. NK cells develop in the bone marrow and constitute about 5-10% of total lymphocytes in the peripheral circulation and secondary lymphoidal or-gans. Effector functions of NK cells include direct natural cytotoxicity, antibody-dependent cellular cy-totoxicity (ADCC), as well as secretion of inflammatory cytokines and chemokines that indirectly regulate the functions of other immune cells .NK cell development occurs in the bone marrow [1] importance of NK cells in anti-viral immunity was first demonstrated by the discovery that patients with a congenital deficiency of NK cells have overwhelming viral infections [2]

2. NK Cell Cytotoxicity

Natural killer (NK) cells are lymphocytes that lack surface expression of T cell receptor/CD3 and Ig thatare important in defense against certain infectious disease. Complete absence of NK cells has been associated with susceptibility to infection with herpes viruses (3, 4) and other viral pathogens (5). A number of receptors on NK cells are capable of mediating cytotoxicity toward tumor cells or virally infected cells without prior sensitization, resulting in the exocytosis of lytic granules (6). This is known as NKcell cytotoxicity, or natural or spontaneous cytotoxicity.

3. Role of NK Cells in the Placentation Process

NK cells are the predominant cell type found in the human placenta in early pregnancy [7]. These cells constitute 60% to 70% of the total lymphocytes in the placenta and are located in the glandular epithelium of the endometrium and around small arteries [8]. The function of the NK cells during this period has not been established; however, the cells are assumed to be essential for placental development and at the maternal-foetal interface. Most hypotheses regarding the potential functions of these cells are derived from detailed investigations performed in mice and humans exhibiting ahaemochorial placenta. In these studies, NK cells were detected during the decidualization of the placenta and participated in endometrial angiogenesis [9]. In cattle, studies have demonstrated that the distribution of lymphocytes was lower in the caruncular and intercaruncular regions of pregnant cows compared with non pregnant cows.

During pregnancy, the architecture of the spiral arteries is significantly modified by angiogenesis, which develops and establishes a flow adequate for decidual development and embryo implantation. The perivascular location of the endometrial NK cells and the detection of vascular endothelial growth factor (VEGF) expression suggest the participation of these cells in the placental development process [10].The remodelling of the spiral arteries is a key characteristic of early placental development in human pregnancy, and the failure of this process has been associated with severe problems and complications during pregnancy, including preeclampsia, foetal growth restriction and miscarriage [11]. The uNK cells are often clustered around the spiral arteries and arterioles during the early phase of pregnancy, and this distribution may reflect the role that uNK cells play in mediating vascular changes during pregnancy [12].

4. A Role of NK Cells in Foetal Development

Several studies have demonstrated numerous aggregates of T and B cells, macrophages, mast cells, and eosinophils in the normal human uterus. However, after implantation, the aggregates of T and B cells disappear, eosinophils and mast cells become scarce, and there is a clear predominance of NK cells and macrophages [13] HLA-G is a molecule of great importance for the regulation of pregnancy and plays a key role in maintaining an immunosuppressive environment for foetal acceptance [14]. The interaction of the HLA-G molecule with inhibitory or activating receptors on the surface of NK cells prevents the lysis of trophoblast cells [15] or activates the production of cytokines that promote the re modelling of the vasculature in the maternal-foetal region, which is important for developing a proper oxygen supply to the foetus [16,17,18]. A new mechanism of immunosuppression by HLA-G has been described in which activated T lymphocytes and NK cells acquire HLA-G via a membrane transfer mechanism termed “trogocytosis”, and these cells exert an immunosuppressive function [19]. HLA-G effectively inhibits cells that could attack the foetus, such as NK cells. NK cells exhibit cytotoxic activity without the prior recognition of an antigen. In addition to expressing activating and inhibitory receptors on their surface, NK cells recognise molecular patterns and are regulated by cytokines [20]. NK cells not only attack cells derived from the foetus though we associate an NK response as harmful to the foetus, these cells play an important role in early pregnancy during vascular formation and the remodelling of the maternal-foetal interface region, allowing formation of the oxygen supply required for foetal development. In late pregnancy, the number of regulatory T lymphocytes and NK cells circulating in the blood decreases [21]

5. Role of NK Cells in the Embryo-Maternal Interaction

During pregnancy, the embryo is recognised by the maternal immune system without triggering an immune response against the permanence and development of the embryo, which occurs under any other circumstances involving exposure to antigens. Therefore, the maternal immune system ensures a favourable environment for the development of the foetus. This phenomenon is termed “immune tolerance” (22).The primary sites of direct contact between the cells derived from the foetus and the maternal

immunocompetent cells is the maternal-foetal interface in the uterus (particularly at the site of implantation), in the maternal arteries, and in the intervillous space in the human placenta(23) .Several factors are involved in this complex immune regulatory network that results in the tolerance and regulation of foetal development and includes the recognition of the paternal major histocompatibility complex (MHC) (expressed by the embryo), the control of the direct cytotoxicity of uNK cells, the activity of regulatory T cells, the release of different cytokines, and the hormonal influence on the maternal immune system (24).Throughout pregnancy, the immune response is modulated at the maternal-foetal interface. In addition to specialised immune cells, cytokines can be derived from the activation of T helper cells and from the activity of macrophages and NK cells in the innate immune response and in the decidual epithelium and placental stroma, which are the sites of partial induction of maternal tolerance(25,26).The MHC class I is critical for antigen presentation to cytotoxic T cells and NK cells and is present in almost all nucleated cells in the body; however, MHC class I is not expressed by the foetal trophoblast cells. This mechanism is crucial for placental and foetal protection against aggression by the maternal immune system (27,28)

The maternal-foetal interface is also characterised by the unique activity of complement regulatory proteins uNK cells, macrophages, T cells of different phenotypes, and cytokines in the local environment [29]. In humans the numbers of T and NK cells increase in the basal decidua (implantation site), suggesting that these cells accumulate at the maternal-foetal interface and play an important role in the maintenance of implantation during pregnancy (30).The actual function of NK cells in the maternal-foetal interface has not been defined clearly; however, several hypotheses have been proposed, such as the control of extravillous invasion, control of uterine vascular remodelling, and local anti-viral action (31).

6. Conclusion

An understanding of normal human NK cells development will enable the pathogenesis of NK cell malignancies to be elucidated. However, the majority of research remains the mouse. Future research into pathogenesisis needed, that specifically integrates observations from patient material with in vivo and in vitro models of human NK cell development[32]

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