

HLA Ib molecules in alloimmunization and inflammatory response

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Today topic is human leukocyte antigen (HLA) non-classical class Ib genes, HLA-G, -E and -F, involved in immune tolerance. HLA-G immune-inhibitory role acting directly on immune cells is extensively documented. HLA-G inhibits natural killer (NK) cytotoxicity. This molecule is also able to negatively influence antigen presentation of dendritic cells (DC), B and T lymphocytes activation and proliferation. HLA-G gene is characterized by few coding alleles and polymorphic regulatory regions, organized in a restricted number of haplotypes (UTR). Both HLA-G genetic polymorphism and expression are correlated to clinical outcome in different pathologies, particularly in inflammatory disease and organ transplantation. HLA-G phylogeny reflects HLA-G haplotype specific association with different clinical conditions. HLA-G sequences associated with immune impairments in pathological conditions are grouped in same phylogenetic clades. Furthermore, this molecule displays several isoforms, soluble or membrane bound, generated by alternative splicing. Besides its expression in immune cells, HLA-G is expressed by the epithelium and is implicated in cell proliferation and differentiation. However, little is known about the qualitative and quantitative HLA-G expression in epithelial cells. HLA-E gene is the least polymorphic of the HLA class Ib genes. While its transcripts have been detected in several tissues, membrane expression appears to be limited in physiological condition to endothelial cells, T and B lymphocytes, macrophages and trophoblast cells. HLA-E peptide-binding groove, composed by $\alpha 1$ and $\alpha 2$ domains, loads highly conserved peptides mainly derived from classical HLA class I leader peptide sequences. HLA-E binds preferentially HLA-G signal peptide. HLA-E inhibit NK cytotoxicity trough the CD94/NKG2A inhibitory receptor. HLA-F appears to be expressed mostly in intracellular compartment; its surface expression is detected on activated B, T, and NK cells in vitro and on extravillous-trophoblast that had invaded the maternal decidua in vivo. HLA-F, expressed as an open conformer molecule, binds the inhibitory receptor KIR3DS1.