HLA

The human leukocyte antigen (HLA) system (the major histocompatibility complex [MHC] in humans) is an important part of the immune system and is controlled by genes located on chromosome 6. It encodes cell surface molecules specialized to present antigenic peptides to the T-cell receptor (TCR) on T cells.

These cell-surface proteins are responsible for the regulation of the immune system.

Classification

The classification of human leukocyte antigen (HLA) molecules is a complex system that categorizes these proteins into various groups and subgroups based on their genetic and structural characteristics. HLA molecules are essential components of the immune system, and their diversity plays a crucial role in immune recognition, transplantation, and disease susceptibility. The two primary classes of HLA molecules are HLA class I and HLA class II.

HLA Class I Molecules: These molecules are found on the surface of almost all nucleated cells in the body. They present fragments of antigens from within the cell to cytotoxic T cells, which can recognize and destroy infected or abnormal cells. HLA class I molecules are further classified into three loci: HLA-A, HLA-B, and HLA-C.

HLA-A: This locus includes various alleles, such as HLA-A01, HLA-A02, and so on. Each allele represents a specific version of the HLA-A gene and is associated with a unique set of amino acid sequences. This diversity is essential for immune recognition.

HLA-B: Similar to HLA-A, HLA-B encompasses numerous alleles, such as HLA-B07, HLA-B44, and many more. These alleles exhibit substantial variation among individuals.

HLA-C: HLA-C alleles, such as HLA-C03 or HLA-C07, are another subset of HLA class I molecules. They also contribute to immune diversity.

HLA Class II Molecules: These molecules are primarily found on antigen-presenting cells, such as dendritic cells, macrophages, and B cells. They present antigens from outside the cell to helper T cells, which play a central role in coordinating the immune response. HLA class II molecules are classified into two loci: HLA-DR and HLA-DQ.

HLA-DR: HLA-DR alleles, such as HLA-DRB101, HLA-DRB103, and so forth, belong to the HLA-DR locus. These alleles are involved in presenting antigens to helper T cells.

HLA-DQ: HLA-DQ alleles, like HLA-DQB102 and HLA-DQB106, are part of the HLA-DQ locus. They also participate in antigen presentation to helper T cells.

In addition to these primary loci, there are other HLA loci, including HLA-DP (for HLA class II) and non-classical HLA loci like HLA-E, HLA-F, and HLA-G, each with its own set of alleles.

The classification of HLA alleles is based on the presence of specific genetic sequences and structural motifs within these molecules. This classification system is essential for various medical applications, including:

Transplantation: Matching the HLA type of a donor and recipient is critical in organ and tissue transplantation to minimize the risk of graft rejection.

Disease Association: Certain HLA alleles are associated with an increased risk of autoimmune diseases, infectious diseases, and drug hypersensitivities.

Pharmacogenomics: HLA variants can influence an individual's response to specific drugs and therapies.

Population Genetics: HLA allele frequencies can be used in population studies and anthropological research to understand human genetic diversity and evolution.

The HLA system is highly polymorphic, meaning that there is a wide variety of alleles within each locus. This diversity contributes to the robustness and adaptability of the immune system but also presents challenges in clinical settings, such as organ transplantation, where finding a compatible donor can be challenging due to HLA diversity.

Synucleinopathy-related disorders such as Lewy body dementia (LBD) and Isolated REM sleep behavior disorder (iRBD) have been associated with neuroinflammation. Yu et al. examined whether the human leukocyte antigen (HLA) locus plays a role in iRBD and LBD. In iRBD, HLA-DRB1*11:01 was the only allele passing FDR correction (OR = 1.57, 95% CI = 1.27-1.93, p = 2.70e-05). They also discovered associations between iRBD and HLA-DRB1 70D (OR = 1.26, 95%CI = 1.12-1.41, p = 8.76e-05), 70Q (OR = 0.81, 95%CI = 0.72-0.91, p = 3.65e-04) and 71R (OR = 1.21, 95%CI = 1.08-1.35, p = 1.35e-03). Position 71 (pomnibus = 0.00102) and 70 (pomnibus = 0.00125) were associated with iRBD. The results suggest that the HLA locus may have different roles across synucleinopathy [1)]

In neurology, psychiatry, and neurosurgery, several human leukocyte antigen (HLA) alleles have been reportedly associated with cutaneous adverse drug reactions (cADRs) induced by antiepileptic drugs, which significantly carry the risk of developing cADRs. Prior to using antiepileptic drugs such as carbamazepine and lamotrigine, which are prone to cause severe cADRs, preemptive HLA genetic testing and therapeutic interventions such as drug selection and dosage adjustment based on the results of the tests can reduce the incidence of cADRs in the population before the initiation of treatment [2)].

Polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) may be different points on a continuum of the same disease. Both have an increased frequency of HLA-DR4 and systemic monocyte activation. 15% of patients with PMR eventually develop GCA.

Juvenile myoclonic epilepsy has strong family history (some studies showing linkage to the HLA region on the short arm of chromosome 6).

see HLA-B27

Moyamoya disease is associated with some HLA antigens (B40 in juvenile form; B54(20) in adult) and anti-double-stranded DNA antibody.

It has been suggested by multiple previous studies that a bunch of Alzheimer disease AD key influencing factors might be attributed to genes encoding human leukocyte antigen (HLA), whose variety is an essential part of human adaptive immunity. A wide range of activities involved in immune responses may be determined by HLA genes, including inflammation mediated by the immune response, T-cell transendothelial migration, infection, brain development and plasticity in AD pathogenesis, and so on. The goal of a article of Wang et al. was to review the recent epidemiological findings of HLA (mainly HLA class I and II) associated with AD and investigate to what extent the genetic variations of HLA were clinically significant as pathogenic factors for AD. Depending on the degree of contribution of HLA in AD pathogenesis, targeted research towards HLA may propel AD therapeutic strategies into a new era of development [3)].

Neuroinflammation commences decades before Alzheimer's disease (AD) clinical onset and represents one of the earliest pathomechanistic alterations throughout the AD continuum. Large-scale genome-wide association studies point out several genetic variants-TREM2, CD33, PILRA, CR1, MS4A, CLU, ABCA7, EPHA1, and HLA-DRB5-HLA-DRB1-potentially linked to neuroinflammation. Most of these genes are involved in proinflammatory intracellular signaling, cytokines/interleukins/cell turnover, synaptic activity, lipid metabolism, and vesicle trafficking. Proteomic studies indicate that a plethora of interconnected aberrant molecular pathways, set off and perpetuated by TNF-α, TGF-β, IL-1β, and the receptor protein TREM2, are involved in neuroinflammation. Microglia and astrocytes are key cellular drivers and regulators of neuroinflammation. Under physiological conditions, they are important for neurotransmission and synaptic homeostasis. In AD, there is a turning point throughout its pathophysiological evolution where glial cells sustain an overexpressed inflammatory response that synergizes with amyloid-β and tau accumulation, and drives synaptotoxicity and neurodegeneration in a self-reinforcing manner. Despite a strong therapeutic rationale, previous clinical trials investigating compounds with anti-inflammatory properties, including non-steroidal anti-inflammatory drugs (NSAIDs), did not achieve primary efficacy endpoints. It is conceivable that study design issues, including the lack of diagnostic accuracy and biomarkers for target population identification and proof of mechanism, may partially explain the negative outcomes. However, a recent meta-analysis indicates a potential biological effect of NSAIDs. In this regard, candidate fluid biomarkers of neuroinflammation are under analytical/clinical validation, i.e., TREM2, IL-1β, MCP-1, IL-6, TNF-α receptor complexes, TGF-β, and YKL-40. PET radio-ligands are investigated to accomplish in vivo and longitudinal regional exploration of neuroinflammation. Biomarkers tracking different molecular pathways (body fluid matrixes) along with brain neuroinflammatory endophenotypes (neuroimaging markers), can untangle temporal-spatial dynamics between neuroinflammation and other AD pathophysiological mechanisms. Robust biomarker-drug codevelopment pipelines are expected to enrich large-scale clinical trials testing new-generation compounds active, directly or indirectly, on neuroinflammatory targets and displaying putative disease-modifying effects: novel NSAIDs, AL002 (anti-TREM2 antibody), anti-Aβ protofibrils (BAN2401), and AL003 (anti-CD33

antibody). As a next step, taking advantage of breakthrough and multimodal techniques coupled with a systems biology approach is the path to pursue for developing individualized therapeutic strategies targeting neuroinflammation under the framework of precision medicine [4].

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