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Genetics multiple sclerosis of patients, inhabitants Yakutia

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Annotation
Results of genetic research on row of gene-candidates determining predisposition to multiple sclerosis disease are given.

For the first time it is shown that disease has reliable association with reception gene CD40 and cytokine gene TNF-α.

Keywords: multiple sclerosis, receptor CD40, cytokine TNFα.

Introduction

Multiple sclerosis is inflammation disease of central neural system, associated by demyelinization neuron and loss neuronal functions. There is supposition, that clue events of disease development is contact cells microglia with activated T-cells, by infiltrating in brain [5,3]. The role of factor that hits oligodendrocytes is cytokine TNF-α, it is secreting by activated microglia with contact T-cells. However, in vivo this process is proceeding more complex. The first, activated microglia of transforming into macrophage may secrete oxygen radicals, straight affective olygodendrocytes [6]. The second, it was shown, that affective factor may be protease active of serum IgG by inducible disease. It is protease active IgG destruct molecules of membrane oligodendrocytes. 90% patients of multiple sclerosis are showing intratecal syntheses IgG, and this is significant criterion of diagnostic. This fact is supposing taking part in development pathogenesis of multiple sclerosis T- and B-cells [2]. Uncover of genetics these interactions may be discover of this disease pathogenesis real picture.

Material and methods

Total number of multiple sclerosis patients in Yakutia equally 150 man, and 30 man out of is Sakha. For research was collected 75 samples of vein blood patients multiple sclerosis which were registered in Center of multiple sclerosis. From collected samples DNA was extracted .
Analyses of the DNA collection was going with total collection DNA of Institute of Chemical Biology and Fundamental Medicine SD RAS. Summary collection of patients of populations West Siberian of region Russian Federation and Republic Sakha was equally 1808 man (normal control – 760, multiple sclerosis – 1048).
Genetic analysis of the collection DNA was made replication genes of variants KIFIB, TNFRSIA, CD40, IL-18, TNF-α and HLA-DRB1.
TNFRSIA, CD40 and HLA-DRB1 genes are coding receptions of immunocompetent cells, responsible for its activation.
Gene KIFIB is coding protein kif1b need for axon growth and it myelinization. Gene IL-18, TNF-α are coding inflammation cytokines, taking part for immune response.
Genetic analysis and statistic processing was made by pharmacogenomics group of Institute of Chemical Biology and Fundamental Medicine of SD RAS.

Results

Research results showed, that variant SNP (rs1800629) gene TNF-α and SNP (rs6074022) gene CD40 was associated with multiple sclerosis (p=0,009 and p=0,00009 accordingly).
While, difference in frequent alleles for other was analyzed genes between of group multiple sclerosis and control was no detected.
Its researching indicate that gene reception CD40, responsible for contact microglia cell with periphery T- lymphocytes, by infiltrating into brain.
This contact is activating microglia and assisting of secretion inflammation cytokine TNF-α [5], and, possible, it is activating B-cells with following forming of plasmatic cells and secreting intratecal IgG. Intratecal synthesis IgG the patiences by European birth was observed in correlation +6/-1 [7]. Symbol (+6) mean six man have synthesis IgG, (-1) – one man have no synthesis.
On table 1 was shown analytic dates for patients of multiple sclerosis, inhabitant on territory Yakutia.
Table 1. Distribution patients of multiple sclerosis by european and sakha birth according to gene TNF-α and CD40.

gene	allele	sakha (n=14)	european (n=61)	total (n=75)
TNFα rs1800629	G	16	110	126
	A	12	12	24
X^2		**14,546: p< 0,005**		
CD40 rs6074022	T	19	72	91
	C	9	32	41
X^2		0,019: p>0,05		

75 patients with multiple sclerosis were analyzed (Sakha – 14, European -61 man).

On the table 1 was shown that patients Sakha and European don't differ on index gene CD40 (X^2 = 0,019; p>0,05). This gene was associated with developing sick of multiple sclerosis. While, index on gene TNF-α does differ trustworthy yakuts from Europeans (X^2 = 14,546; p<0,005). Patients of sakha did not associate with TNF- α gene. Possibly, with this are relate low correlation of intratecal synthesis IgG at sakha (+1/-4). This correlation are typical for Asiatic population.

How-ever, this correlation at european patients are residing in Yakutia, also low (+2/-1), as compared with patients from southern origin (+6/-1).

Possibly, climatic condition in Yakutia influence on mechanic processes of pathogeneses multiple sclerosis.

Discussion

Sophie Chabot [5] with group researchers proposed the schema of taking part genes CD40 and CD40L in activating of microglia (figure.1). It does carry out by contact of receptors CD40 and CD23 with its ligands CD4 T- lymphocytes of blood by infiltrating into brain. It seen that receptor CD40 on microglia serves as an amplifier of inflammatory response in the brain.

Under resting condition, the level of CD40 on microglia is relatively low, but is markedly increased upon challenge with cytokines IFN-g, and some worse TNF- α and lipopolysaccharide.

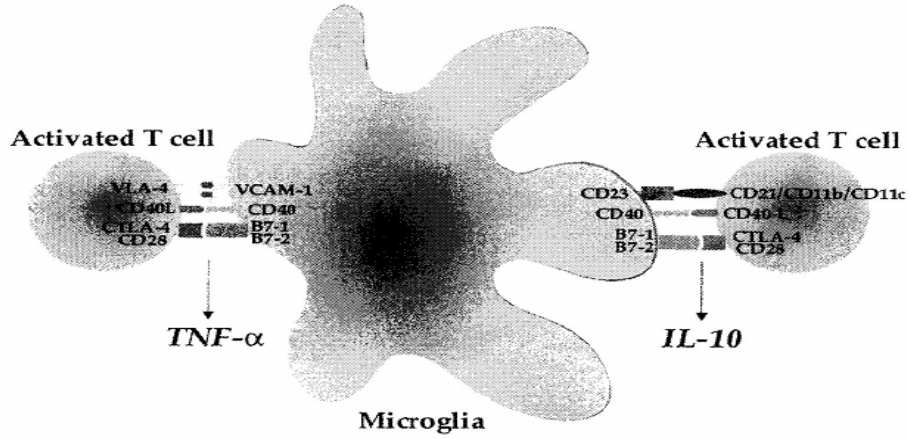

Figure 1. Cell complex: microglia – T lymphocytes (Th1 and Th2) [5]

CD4 T-cells have ligants CD40L and CD23L. Activated cell complex are secreting cytokines TNF- α and IL10. These cytokine are antagonist, and that's dominating secretion one carry out inhibition other. Balance between action inflammation TNF-α and anti-inflammation IL10 are be conditioned of clinic patience. Cell complex must include B-cell (contact CD4 T-cell with reception CD40 B-cell). Activated B-cell of transformed to plasmatic cell and produce IgG. Difference on cytokine TNF- α , and also in correlation intratecal of olygoclonal synthesis IgG by patience sakha, apparently, be accounted by dominating IL10 and about inhibiting action TNF- α .

Formation of inflammatory cell complex with serum T-cells are evidence straight of taking part adaptive immunity of organizer, by was acquired of effect exogenic factors (infection or other) on background of genetic preposition to disfuction of immune system.

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