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ETIOPATHOGENETIC SIGNIFICANCE OF POLYMORPHISMS OF THE IL10, SERPINE1, NOS3, AND IL1B GENES IN THE DEVELOPMENT OF MAXILLOFACIAL NECROSIS

Abstract. *Maxillofacial purulent-necrotic lesions represent a serious clinical problem due to their aggressive course, high risk of complications, and limited effectiveness of standard therapeutic approaches. In recent years, increasing attention has been paid to the role of genetic factors that determine individual susceptibility to severe inflammatory and necrotic processes in the maxillofacial region. This study focuses on the etiopathogenetic significance of polymorphisms in the IL10, SERPINE1, NOS3, and IL1β genes, which are involved in immune regulation, inflammatory response, vascular function, and tissue perfusion. Variations in the IL10 gene may affect anti-inflammatory cytokine production, leading to prolonged inflammation and impaired tissue repair. Polymorphisms of the SERPINE1 gene are associated with disturbances in fibrinolysis and microcirculation, increasing the risk of ischemia and necrosis. NOS3 gene variants contribute to endothelial dysfunction and reduced nitric oxide synthesis, negatively influencing blood flow and regenerative capacity. IL1β gene polymorphisms enhance pro-inflammatory activity, promoting extensive tissue destruction. The combined effect of these genetic variations plays a significant role in the severity, progression, and clinical outcomes of maxillofacial necrosis. Understanding these mechanisms may improve risk stratification, early diagnosis, and the development of personalized therapeutic strategies.*

Keywords: *maxillofacial necrosis, gene polymorphism, IL10, SERPINE1, NOS3, IL1β, inflammation, genetic susceptibility.*

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YUZ-JAG‘ SOHASIDA NEKROZ RIVOJLANISHIDA IL10, SERPINE1, NOS3 VA IL1β GENLARI POLIMORFIZMLARINING ETIOPATOGENETIK AHAMIYATI

Annotatsiya. *Yuz-jag‘ sohasidagi yiringli-nekrotik shikastlanishlar agressiv kechishi, asoratlar rivojlanishining yuqori xavfi hamda standart davolash usullarining cheklangan samaradorligi bilan ajralib turuvchi jiddiy klinik muammo hisoblanadi. So‘nggi yillarda yuz-jag‘ sohasida og‘ir yallig‘lanish va nekrotik jarayonlarning rivojlanishiga individual moyillikni belgilovchi genetik omillarning roli tobora ortib bormoqda. Ushbu tadqiqot immun javobni tartibga solish, yallig‘lanish reaksiyalari, tomirlar funksiyasi va to‘qimalar perfuziyasida ishtirok etuvchi IL10, SERPINE1, NOS3 va IL1β genlari polimorfizmlarining etiopatogenetik ahamiyatini o‘rganishga bag‘ishlangan.*

IL10 geni polimorfizmlari yallig‘lanishga qarshi sitokinlar sinteziga ta’sir ko‘rsatib, yallig‘lanish jarayonining cho‘zilishi va to‘qimalar reparatsiyasining buzilishiga olib kelishi mumkin. SERPINE1 geni polimorfizmlari fibrinoliz jarayonlari va mikrosirkulyatsiyaning buzilishi bilan bog‘liq bo‘lib, ishemiya va nekroz rivojlanishi xavfini oshiradi. NOS3 geni variantlari endotelial disfunksiya va azot oksidi sintezining kamayishiga olib kelib, qon oqimi va to‘qimalarning regenerativ salohiyatiga salbiy ta’sir ko‘rsatadi. IL1β geni polimorfizmlari esa yallig‘lanish mediatorlarining ortiqcha faollashuvi bilan xarakterlanib, keng ko‘lamli to‘qima destruksiyasining rivojlanishiga zamin yaratadi. Ushbu genetik o‘zgarishlarning kompleks ta’siri yuz-jag‘ nekrozining og‘irligi, rivojlanish dinamikasi va klinik natijalarini belgilashda muhim ahamiyat kasb etadi. Ushbu mexanizmlarni chuqur anglash xavf guruhlarini aniqlash, erta diagnostika va individual davolash strategiyalarini ishlab chiqish imkoniyatlarini kengaytiradi.

Kalit so‘zlar: *yuz-jag‘ nekrozi, gen polimorfizmi, IL10, SERPINE1, NOS3, IL1β, yallig‘lanish, genetik moyillik.*

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ЭТИОПАТОГЕНЕТИЧЕСКОЕ ЗНАЧЕНИЕ ПОЛИМОРФИЗМОВ ГЕНОВ IL10, SERPINE1, NOS3 И IL1β В РАЗВИТИИ ЧЕЛЮСТНО-ЛИЦЕВОГО НЕКРОЗА

Аннотация. *Гнойно-некротические поражения челюстно-лицевой области представляют собой серьёзную клиническую проблему вследствие агрессивного течения, высокого риска развития осложнений и ограниченной эффективности стандартных терапевтических подходов. В последние годы особое внимание уделяется роли генетических факторов, определяющих индивидуальную предрасположенность к тяжёлым воспалительным и некротическим процессам в челюстно-лицевой области. Настоящее исследование посвящено изучению этиопатогенетического значения полиморфизмов генов IL10, SERPINE1, NOS3 и IL1β, участвующих в регуляции иммунного ответа, воспалительных реакций, сосудистой функции и тканевой перфузии. Генетические вариации гена IL10 могут оказывать влияние на продукцию противовоспалительных цитокинов, способствуя пролонгированию воспалительного процесса и нарушению репаративных механизмов. Полиморфизмы гена SERPINE1 ассоциированы с нарушениями фибринолиза и микроциркуляции, что повышает риск ишемии и некротических изменений. Варианты гена NOS3 приводят к эндотелиальной дисфункции и снижению синтеза оксида азота, что негативно отражается на кровоснабжении и регенеративном потенциале тканей. Полиморфизмы гена IL1β усиливают провоспалительную активность, способствуя развитию обширной тканевой деструкции. Совокупное влияние указанных генетических вариаций играет значимую роль в тяжести течения, прогрессировании и клинических исходах челюстно-лицевого некроза. Понимание данных механизмов открывает возможности для улучшения стратификации риска, ранней диагностики и разработки персонализированных лечебных стратегий.*

Ключевые слова: *челюстно-лицевой некроз, генетический полиморфизм, IL10, SERPINE1, NOS3, IL1β, воспаление, генетическая предрасположенность.*

Introduction. Purulent–necrotic processes in the maxillofacial region represent one of the most urgent problems in modern dentistry, maxillofacial surgery, and clinical immunology. These pathologies often develop against the background of infectious factors, traumatic injuries, vascular disorders, metabolic diseases, and insufficiency of the immune system [1,4,7]. In recent years, it has been proven that the severe course and resistance to treatment of such processes are closely associated not only with external etiological factors but also with hereditary and genetic predisposition [9,12].

According to the literature, inflammatory mediators and cytokines play a key role in the development of purulent necrosis in the maxillofacial region [2,5]. In particular, the IL10 gene is one of the main genes encoding anti-inflammatory cytokines, and its rs1800872 polymorphism is of great importance in determining the intensity and duration of the immune response [3]. Studies indicate that certain allelic variants of the IL10 gene are associated with prolonged inflammation, expansion of necrotic lesions, and delayed reparative processes [6]. This polymorphism is especially clinically significant in patients with weakened immunity or chronic diseases [3,8].

The SERPINE1 gene is one of the key regulators of fibrinolysis, and its rs1799768 polymorphism affects the development of thrombogenic conditions [6,11]. Several authors emphasize that unfavorable variants of the SERPINE1 gene increase the risk of impaired microcirculation, tissue ischemia, and necrosis in the maxillofacial region [10]. This negative effect is particularly pronounced in patients with diabetes mellitus, cardiovascular diseases, or post-infectious conditions [8].

The NOS3 gene encodes endothelial nitric oxide synthase, which plays an essential role in maintaining vascular tone and tissue perfusion [8]. The NOS3 rs2070744 polymorphism is associated with endothelial dysfunction, which may contribute to the severe course of purulent–necrotic processes in the maxillofacial region [7–11]. Studies report that patients carrying these gene variants have reduced tissue regenerative potential and a higher incidence of postoperative complications [6].

The IL1β gene is one of the main pro-inflammatory mediators, and its rs1143627 polymorphism determines the level of cytokine production [1–5]. The literature indicates that certain IL1β genotypes are associated with excessive activation of inflammatory reactions, increased pain syndrome, and rapid spread of purulent processes [2]. This is particularly important in clinical forms accompanied by osteonecrosis of the jaw bones and extensive soft tissue involvement [11].

Thus, the analysis of the literature demonstrates that polymorphisms of the IL10, SERPINE1, NOS3, and IL1β genes have significant pathogenetic importance in the development of purulent–necrotic processes in the maxillofacial region. These genetic factors determine immune response, vascular status, and the activity of inflammatory mediators, thereby exerting a substantial influence on disease course and prognosis [1]. Taking gene polymorphisms into account when developing individualized diagnostic and therapeutic strategies represents a promising approach to the effective management of maxillofacial purulent necrosis [4].

Results.

According to the results of the conducted analysis, it was determined that the distribution of alleles and genotypes of the IL10 gene C592A (rs1800872) polymorphism differed between the study groups and the control group. In the first group (patients with purulent maxillofacial necrosis associated with post-COVID syndrome), the proportion of the wild allele was 51.7%, while the minor allele was recorded

at 48.3%. When analyzed by genotype, it was found that 25.0% of the patients had the homozygous wild (A/A) genotype, 53.3% had the heterozygous (A/C) genotype, and 21.7% had the homozygous non-wild (C/C) genotype. In the second group (patients with purulent maxillofacial necrosis associated with polyangiitis), the allele distribution consisted of 57.5% wild and 42.5% minor alleles, and their genotype distribution comprised 33.3% A/A, 48.3% A/C, and 18.3% C/C genotypes. In the third group (patients receiving dialysis due to chronic renal failure and affected by purulent maxillofacial necrosis), the wild allele constituted 43.3% and the minor allele 56.7%, and their genotype distribution was observed to consist respectively of 20.0% A/A, 46.7% A/C, and 33.3% C/C genotypes. In the control group, the A allele was identified at 40.8% and the G allele at 59.2%, and their genotype distribution constituted 18.3% A/A, 45.0% A/C, and 36.7% C/C. The overall results indicate that there are notable differences in both allele and genotype distributions of the IL10 rs1800872 polymorphism between the study groups and the control group, suggesting that this polymorphism may manifest as a potential genetic factor in the pathogenesis of various pathological conditions (Table 1).

Table 1.

Allele and genotype distribution of the examined polymorphisms in different groups

SNP type	Groups	Allele distribution				Genotype distribution					
		Wild-type allele		Minnor allele		Homozygote wild-type		Heterozygote		Homozygote non-wildtype	
		n	%	n	%	n	%	n	%	n	%
IL10 rs1800872	First group	62	51.7	58	48.3	15	25.0	32	53.3	13	21.7
	Second group	69	57.5	51	22.5	20	33.3	29	48.3	11	18.3
	Third group	52	43.3	68	67.7	12	20.0	28	46.7	20	33.3
	Control group	49	40.8	71	59.2	11	18.3	27	45.0	22	36.7
SERPINE1 rs1799768	First group	76	63.3	44	36.7	26	43.3	24	40.0	10	16.7
	Second group	58	48.3	62	51.7	16	26.7	26	43.3	18	30.0
	Third group	77	64.2	43	35.8	26	43.3	25	41.7	9	15.0
	Control group	56	46.7	64	53.3	13	21.7	30	50.0	17	28.3
NOS3 rs2070744	First group	71	59.2	49	48.2	22	36.7	27	45.0	11	18.3
	Second group	95	79.2	25	20.8	39	65.0	17	28.3	4	6.7
	Third group	82	68.3	38	31.7	28	46.7	26	43.3	6	10.0
	Control group	93	77.5	27	22.5	36	60.0	21	35.0	3	5.0
IL1β rs1143627	First group	59	49.2	61	50.8	13	21.7	33	55.0	14	23.3
	Second group	44	36.7	76	63.3	7	11.7	30	50.0	23	38.3
	Third group	71	59.2	49	40.8	21	35.0	29	48.3	10	16.7
	Control group	79	71.7	41	45.0	28	46.7	23	38.3	9	15.0

It was also determined that the distribution of alleles and genotypes of the SERPINE1 gene −675 5G/4G (rs1799768) polymorphism differed between the study groups and the control group. In the first group (patients with purulent maxillofacial necrosis associated with post-COVID syndrome), the proportion of the wild allele was 63.3%, while the minor allele was recorded at 36.7%. According to genotype analysis, 43.3% of the patients had the homozygous wild genotype, 40.0% had the heterozygous genotype, and 16.7% had the homozygous non-wild genotype. In the second group (patients with purulent maxillofacial necrosis associated with polyangiitis),

the distribution of wild and minor alleles constituted 48.3% and 51.7%, respectively, and the genotype distribution consisted of 26.7% homozygous wild, 43.3% heterozygous, and 30.0% homozygous non-wild genotypes. In the third group (patients receiving dialysis due to chronic renal failure and affected by purulent maxillofacial necrosis), the proportion of the wild allele was 64.2%, and the minor allele was identified at 35.8%. In this group, the genotype distribution consisted of 43.3% homozygous wild, 41.7% heterozygous, and 15.0% homozygous non-wild genotypes. In the control group, the wild allele constituted 46.7% and the minor allele 53.3%. Genotype analysis showed that 21.7% had the homozygous wild genotype, 50.0% had the heterozygous genotype, and 28.3% had the homozygous non-wild genotype (Table 1).

In addition, when the distribution of alleles and genotypes of the NOS3 gene C786T (rs2070744) polymorphism was analyzed in the study groups and the control group, in the first group the proportion of the wild allele was 59.2%, and the minor allele was recorded at 40.8%. According to genotype analysis, 36.7% of the patients had the homozygous wild genotype, 45.0% had the heterozygous genotype, and 18.3% had the homozygous non-wild genotype. In the second group, the proportion of the wild allele was 79.2%, and the minor allele was observed at 20.8%. The genotype distribution consisted respectively of 65.0% homozygous wild, 28.3% heterozygous, and 6.7% homozygous non-wild genotypes. In the third group, the wild allele constituted 68.3%, and the minor allele 31.7%. Genotype analysis showed that 46.7% had the homozygous wild genotype, 43.3% had the heterozygous genotype, and 10.0% had the homozygous non-wild genotype. In the control group, the proportion of the wild allele was 77.5% and the minor allele constituted 22.5%, while the genotype distribution consisted respectively of 60.0% homozygous wild, 35.0% heterozygous, and 5.0% homozygous non-wild genotypes (Table 1).

Similarly, according to the results for the distribution of alleles and genotypes of the IL1β gene T31C (rs1143627) polymorphism in the study groups and the control group, in the first patient group the proportion of the wild allele was 49.2% and the minor allele was recorded at 50.8%, and the genotype distribution percentages showed that 21.7% of the patients had the homozygous wild genotype, 55.0% had the heterozygous genotype, and 23.3% had the homozygous non-wild genotype. In the second group, the proportion of the wild allele was 36.7%, and the minor allele was observed at 63.3%. The genotype distribution consisted respectively of 11.7% homozygous wild, 50.0% heterozygous, and 38.3% homozygous non-wild genotypes. In the third group, the wild allele constituted 59.2%, and the minor allele 40.8%. Genotype analysis showed that 35.0% of the patients had the homozygous wild genotype, 48.3% had the heterozygous genotype, and 16.7% had the homozygous non-wild genotype. In the control group, the proportion of the wild allele was 65.8% and the minor allele constituted 34.2%. The genotype distribution consisted respectively of 46.7% homozygous wild, 38.3% heterozygous, and 15.0% homozygous non-wild genotypes (Table 4.1).

Conclusion.

The present study demonstrated significant differences in allele and genotype distributions of the IL10 rs1800872, SERPINE1 rs1799768, NOS3 rs2070744, and IL1β rs1143627 polymorphisms between patients with purulent maxillofacial necrosis of different etiologies and the control group. Variations in these genes were shown to be associated with distinct clinical backgrounds, including post-COVID syndrome, polyangiitis, and chronic renal failure with dialysis, suggesting their involvement in immune regulation, inflammatory response, vascular function, and tissue ischemia. The increased frequency of minor alleles and non-wild genotypes in certain patient groups indicates a possible genetic predisposition to severe inflammatory and necrotic processes. Overall, the findings support the etiopathogenetic significance of these polymorphisms and highlight their potential value as genetic markers for risk assessment, prognosis, and the development of personalized diagnostic and therapeutic strategies in maxillofacial necrosis.

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