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Moleculobiological Characteristics of Oral Squamous Cell Carcinomas

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SUMMARY

Oral squamous cell carcinomas (OSCCs) are associated with poor prognosis, and despite advances in therapy approaches, no major improvement in survival has been achieved in the recent years. Efforts are now directed toward finding new biological markers that could predict tumor behavior more accurately. OSCCs, as the majority of malignant tumors, arise from progressive accumulation of genetic and epigenetic lesions, transforming normal cells into malignant. In this paper, an analysis of current studies directed to understanding the underlying mechanisms of OSCC pathogenesis was presented. The emphasis was put on mutational analysis of cancer genes, as well as on the role of viral infections and methylation processes in OSCC. Finally, an overview of studies that tried to determine the possibility for developing OSCC was given.

Keywords: oral carcinomas; carcinogenic genes; viral infections; hipermethylation; predisposition

INTRODUCTION

Oral squamous cell carcinomas (OSCCs) are invasive epithelial neoplasm with various degree of squamous differentiation and penchant for early and extensive metastases into the lymph nodes. They are predominantly present in middle-aged people (the fifth and sixth decades) who consume alcohol and tobacco. Their origin is squamous epithelium and epidermal keratinocytes, and the most prevalent sites for OSCC are lips, mouth, tongue, salivary glands, gums, oropharynx, and other places within the oral cavity. OSCC represent about 90-95% of mouth cancers, while the remaining 5-10% of malignant tumors are tumors of minor salivary glands, malignant melanomas and soft tissue sarcomas. OSCC mainly occur in people older than 50 years, and rarely in younger than 40 years (1-6%), although the trend observed in recent years shows an increased incidence of cancer in much younger age. They are two to three times more common in men than in women, and the occurrence of disease so far has been mostly associated with smoking and regular alcohol consumption. The etiological factors also include certain viruses, UV radiation, genetic factors, and others [1, 2, 3].

Rapid growth and propensity for metastasis, as well as five-year survival rate of only 34% in case of present metastases make oral cancer one of the major sociomedical problems. Great intellectual efforts and financial resources are invested in tumor research in order to achieve better understanding of their biology that will lead to precise and accurate diagnosis and prediction of patient response to the treatment. Very important research in the field of molecular biology is developing in different directions (some will be mentioned later), important studies are related to genetics and epigenetics. From the aspect of molecular biology, neoplastic transformation is a multistage process of tissue homeostasis disturbance leading to uncontrolled cell proliferation and inhibition of cell death by apoptosis. Each level is characterized by genetic and epigenetic changes and their progressive accumulation lead to transformation of normal cell into malignant.

GENETIC BASIS OF OSCC

Cell division is precisely controlled by genes whose protein products constitute the complex network responsible for receiving, transmitting and final realization of signal for mitosis. The expansion of clone or cell mass is manifested at clinical level as neoplasia and it is caused by structural and functional lesions of specific genetic loci, called „carcinogenic genes". Two key groups of genes that, according to their characteristics, deserve this epithet are: a) oncogenes or mutated forms of normal cellular genes, protooncogenes, present in most eukaryotic genomes; and b) tumor-suppressor genes – anti-oncogenes or inhibitors of uncontrolled growth and proliferation of cells, and thus the malignant phenotype. There are also genes responsible for the correction of endogenously and/or exogenously

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induced lesions in genetic material – DNA rapper genes or genes that present the first line for defense of human genome integrity, but they will not be the subject of this paper [4-7].

Cell homeostasis is maintained by the balance that exists between these two classes of genes. With concurrent activation of oncogenes and inactivation of tumor suppressor genes this homeostasis is violated and tumors are developing. From the perspective of the mechanism of pathogenesis and possible therapeutic interventions, it is important to determine the time and the gene activated/inactivated in the process of malignant transformation.

Oncogenes

Oncogenes are genes whose protein products stimulate cell growth, division and differentiation through the process of signaling for transduction and transcription regulatory mechanism (Figure 1). In the form of proto-oncogenes (regular, non-mutated) they show strictly controlled temporal and spatial expression. The mutation of proto-oncogenes gives oncogenes, which are uncontrollably expressed. These mutations may include: point mutations, gene deletions, gene amplification and chromosome rearrangements (mainly translocations).

Some of the oncogenes that have proven the role in the pathogenesis of OSCC are H-ras, c-myc and c-erbB-2. They are the key players in one of the central cell signaling paths that lead to uncontrolled proliferation (Figure 2).

By position and function, the protein products of the family genes ras (H, K, N) belong to the group of membrane G-proteins, which are spatial and functional connection between the receptors that receive the mitose signal and cytoplasmic protein kinase to which it is transmitted. The frequency of H-ras mutations in OSCC varies and ranges from 5% in Western countries up to 35% in Asian population. In our population, the frequency of H-ras mutation is 22% [8], provided that in the subgroup of patients who have vermilion cancer, the percentage is even higher (55%). It is interpreted by the synergism of three risk factors-tobacco, alcohol and UV radiation [9]. It is also believed that mutations in H-ras gene are an early event in the development of oral as well as head and neck tumors because they are observed even in some premalignant lesions [10, 11].

Protein product of c-erbB-2 gene is a transmembrane protein that is also involved in the genesis of proliferative signals from the plasma membrane to the nucleus. Oncogenic activation of c-erbB-2 gene occurs most frequently due to increase in its copy, ie. gene amplification, which results in activation of transmembrane oncoprotein, and the initiation of proliferative signals in the absence of growth factors. Activation of c-erbB-2 oncogene leads to immortalization and transformation of cells in vitro and was also detected in different human tumors. In OSCC, data obtained for alterations in c-erbB-2 gene, depending on the applied methods, range from 20% to 80% [12, 13]. In our patients with OSCC, in 45% of cases, mutation was present in c-erbB-2 gene, of which 32% were amplifications and 13% deletions [8]. Random increase or decrease of the number of gene copies indicates the presence of genomic instability which is a key phenomenon in the pathogenesis of tumor [11]. Regardless of some controversy, most authors think that c-erbB-2 gene has a role in the advanced stage of disease.

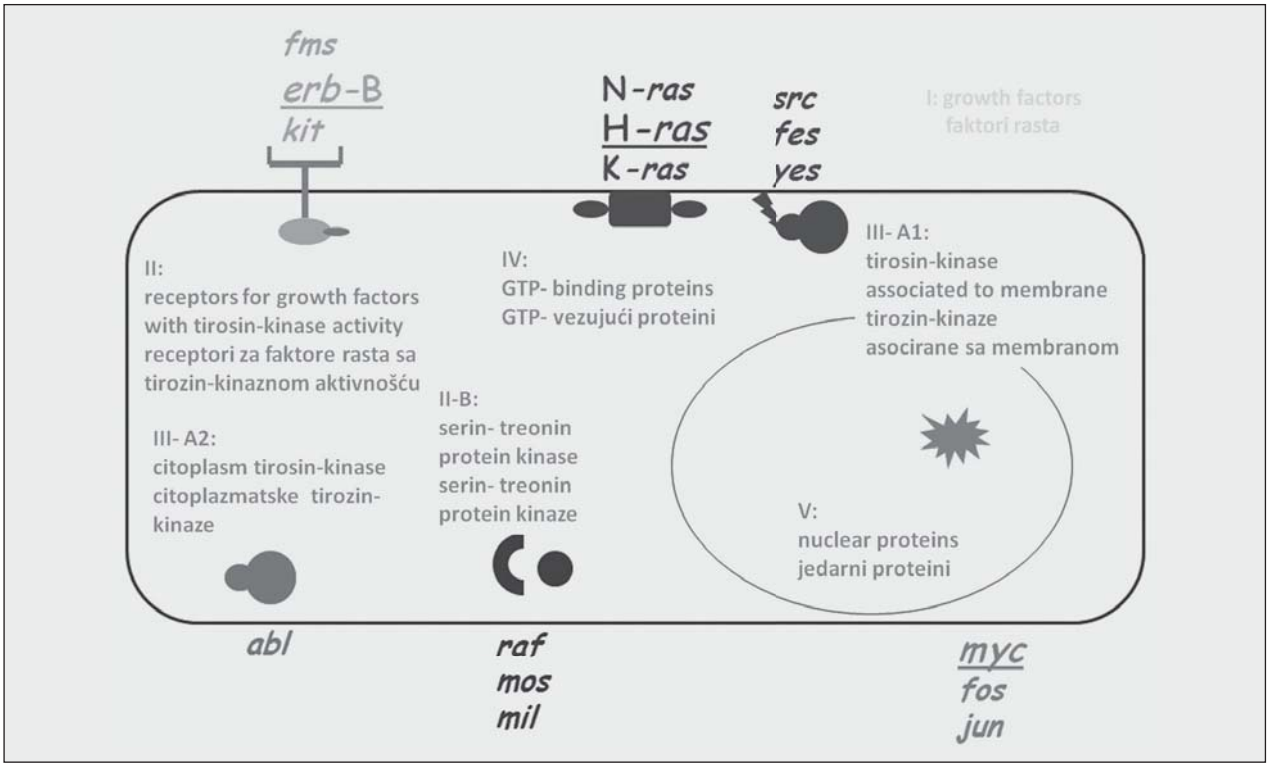

Figure 1. Cellular localization of oncogene products (oncoproteins) – located outside the cell, in the cell membrane, cytoplasm and nucleus
Slika 1. Ćelijska lokalizacija produkata onkogena (onkoproteina) – nalaze se van ćelije, u ćelijskoj membrani, citoplazmi i jedru

Expression of c-myc gene is also changed in various human malignancies. Protein product of this gene is a DNA-binding, nuclear protein that modulates the activity of multiple genes involved in processes of cell cycle. Therefore, as a transcription factor, it achieves regulatory activities in the important processes such as stimulation of proliferation, inhibition of differentiation and increased sensitivity to the apoptotic stimuli [14]. Based on available data from the literature, c-myc amplification is found in 20 to 40% of oral cancers in Europe and America, and data for our population fit into these numbers while in Asia this percentage is close to 70% [8, 15, 16]. Similarly to c-erb oncogene, c-myc is frequently mutated (amplified) in tumors of higher histological grade, poorly differentiated and those with metastasis.

Tumor-suppressor genes

Tumor-suppressor genes (anti-oncogenes) are genes which protein products inhibit neoplastic transformation, by preventing cell division if there is damage of the genetic material. They are involved in cell cycle control, by preventing progression through the cell cycle until the damage is repaired, and if damages are extensive, they lead to activation of programmed cell death-apoptosis. Mutations in tumor suppressor genes result in disruption of cell cycle control.

The most important gene in this group is the TP53 gene. Maintaining stability and integrity of the cell genome is the basic biological function of TP53 gene and TP53 protein. According to the literature, this protein is a key transcription factor or biomolecule that restrains division of the cell with damaged genetic material by its regulatory activity (Figure 2). It is also a gene commonly mutated in many human tumors- almost 70% of human solid tumors [17]. Numerous studies show that frequency of mutations in this gene in cancers of the head and neck is about 60% in Europe and America. It is much lower in Asian population and is associated to different lifestyle [18]. Data obtained for our patients with OSCC are in compliance with the date from literature for the western population (60%) [8, 19]. In our patients, the inactivation of TP53 caused by mutations increases with the progression of the disease. Therefore, the frequency of mutations is higher in moderately and poorly differentiated tumors (G2 and G3) compared to well differentiated (G1), as well as in more invasive (T3 and T34) as compared to less invasive (T1 and T2) [20]. Numerous studies from different geographic regions also found a correlation between the presence of TP53 mutations and tobacco consumption, but in our population, this relationship is not confirmed. Beside TP53, the changes in other tumor suppressor genes, such ash Rb and p16 are associated to OSCC [21].

VIRUSES AND THE PATHOGENESIS OF OSCC

Viral infections and infections with oncogenic types of human papilloma virus (HPV16 and HPV18) which role in development of cervical cancer has been known for long time recently become associated to the pathogenesis of OSCC. It is interesting to mention that HPV positive and HPV negative tumors are considered as different clinical entities. An important mechanism of action of HPV is that the products of viral genome, E6 and E7 oncoproteins,

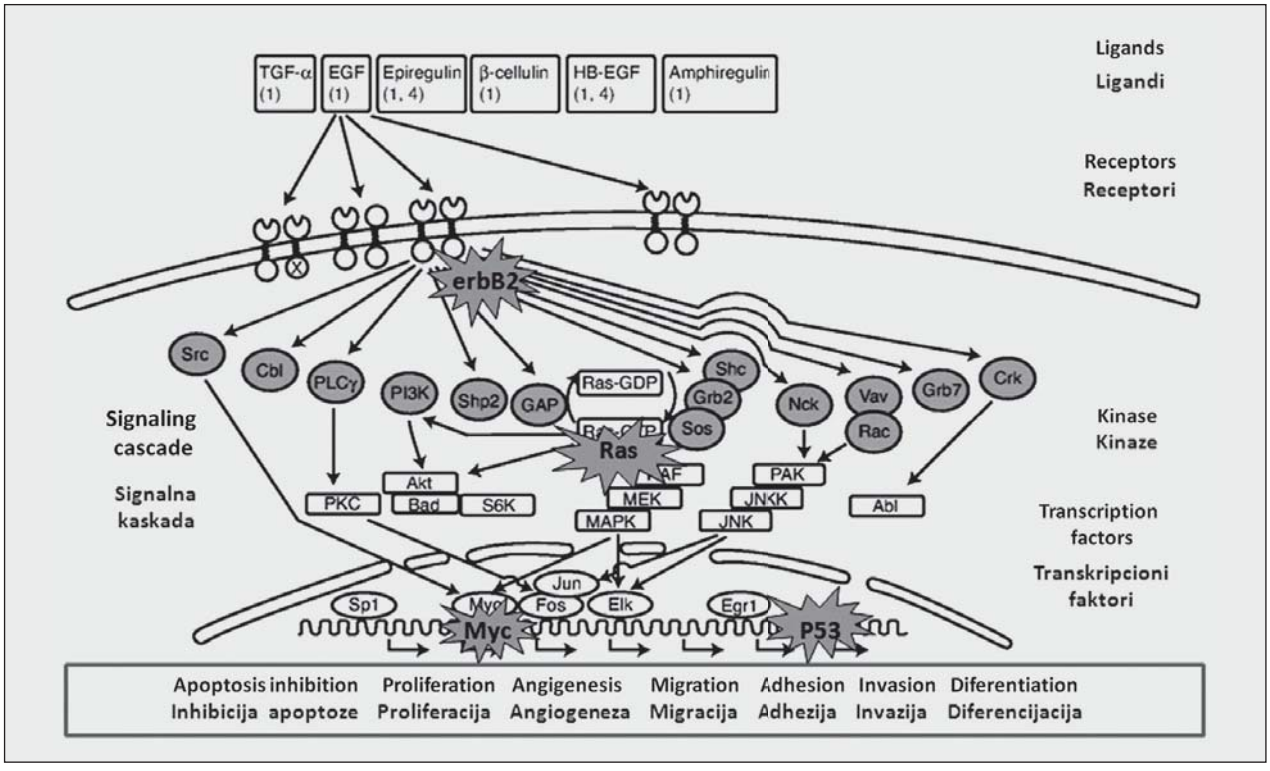

Figure 2. Possible signal transduction pathways important for pathogenesis of OSCC
Slika 2. Mogući putevi signalne transdukcije značajne za patogenezu OSCK

inactivate key tumor suppressor genes TP53 and Rb, and give the signal for the uncontrolled cell division [21, 22].

The extreme disparity in world's literature data about the importance of HPV infection in the pathogenesis of OSCC has led researchers to propose two etiopathogenetic mechanisms: HPV+ and HPV-. Head and neck cancers, where viruses were detected in, did not show mutations in tumor suppressor genes (TP53, Rb, etc.) (or extremely rarely) meaning that the loss of function of tumor suppressor resulted from the interaction with viral oncoproteins, and not as the consequence of mutation. It is interesting that the data even at the level of our population is contradictory. One study found a low prevalence of HPV infection in OSCC in Serbia and believes that the predominant route of carcinogenesis is HPV- [8], while the other study found high incidence of HPV infections [23].

THE ROLE OF METHYLATION

DNA methylation is an epigenetic mechanism for negative regulation of transcription and gene expression (gene silencing), which was recently considered in carcinogenesis. The correct form of DNA methylation is necessary prerequisite for normal cell functioning. Interfering with the usual pattern of DNA, methylation can cause changes in important cellular mechanisms, such as control of cell cycle, DNA repair, drug resistance, apoptosis and angiogenesis. Disturbed pattern of methylation is one of the characteristics of tumor cells. A large number of human diseases is associated with aberrant DNA methylation. The latest data show the importance of the phenomenon of global methylation in early stages of oral carcinogenesis, one that includes HPV infection as well as carcinogenesis caused by tobacco and alcohol and independent of HPV [24]. In our population hipermethylation of key tumor suppressor genes (p16, DAPK, APC, etc.) was studied and the conclusion was that aberrant methylation is common in OSCC [25].

PREDISPOSITION FOR THE DEVELOPMENT OSCC

"Carcinogenic genes" and somatic changes in tumor tissue were subjects of numerous studies for many years. Recently, an attention has been brought to the studies on genetic constitution of individuals in attempt to find elements that make someone more or less prone to certain diseases, including OSCC. The differences that exist within a particular DNA locus between individuals of one species are designated as DNA polymorphisms and include polymorphic nucleotide sequence and polymorphism in the length of sequence. Polymorphisms in nucleotide sequences may be related to variability in base substitution and these are dot polymorphisms (SNP) or linked to insertion or deletion of a sequence of nucleotides. Functional polymorphisms affect the expression of genes they are located in, and it is expected to reflect the function of a given protein/enzyme and processes these enzymes are involved in. Association studies are used to assess the presence of gene polymorphisms with the occurrence of disease. This analysis is based on comparison of the frequency of a given polymorphism in the population of affected individuals with the appropriate frequency of polymorphism in a population of healthy people. Some polymorphisms have proved to be useful markers in determining risk of developing disease, its course and response to therapy.

Polymorphisms, such as functional polymorphisms in genes that control cell proliferation and cell death, DNA repair systems, and others are generally accepted as modulators of carcinogenic risk. As a potential markers in susceptibility for the development of OSCC, polymorphisms in genes responsible for inflammatory reactions (genes for cytokines), metabolism of xenobiotics, detoxification (glutathione transferase genes) etc. are also interesting [26-29].

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Molekularnobiološke osobine oralnih skvamocelularnih karcinoma

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KRATAK SADRŽAJ

Oralne skvamocelularne karcinome (OSCK) odlikuje uglavnom loša prognoza i, uprkos pomacima u terapijskim postupcima, poslednjih godina nije ostvaren napredak u preživljavanju osoba s ovim tumorom. Velike nade se polažu u molekularnu medicinu i pronalaženje novih bioloških markera pomoću kojih bi preciznije nego što to dopuštaju klinički i histopatološki parametri moglo da se predvidi ponašanje tumora. OSCK, kao i većina drugih malignih oboljenja, rezultat su postupne akumulacije raznovrsnih genetičkih i epigenetičkih promena u ćelijama, koje od normalnih postaju neoplastične. U ovom radu dat je presek nekih od pravaca istraživanja na polju molekularne biologije oralnih karcinoma, s osvrtom na studije koje se bave ispitivanjem somatskih mutacija u kancerskim genima, učešćem onkogenih virusa u patogenezi i značaju procesa metilacije za OSCK. Takođe su pomenute studije posvećene utvrđivanju eventualnog postojanja predispozicije za razvoj OSCK.

Ključne reči: oralni karcinomi; kancerski geni; virusna infekcija; hipermetilacija; predispozicija

UVOD

Oralni skvamocelularni karcinomi (OSCK) su invazivne epitelne neoplazme s različitim stepenom skvamozne diferencijacije i sklonošću ka ranim i ekstenzivnim metastazama u limfne čvorove. Pretežno se razvijaju kod sredovečnih osoba koje konzumiraju alkoholna pića i puše. Potiču od pločasto-slojevitog epitela, odnosno epidermnih keratinocita, a predilekciono mesto nastanka su usne, pod usne duplje, jezik, pljuvačne žlezde, desni, orofarinks i druga mesta u ustima. Čine 90-95% kancera usne duplje, dok su preostalih 5-10% maligni tumori malih pljuvačnih žlezda, maligni melanomi i sarkomi mekih tkiva. OSCK se uglavnom javljaju kod osoba starijih od 50 godina, retko kod mladih ljudi (1-6%), iako se poslednjih godina zapaža tendencija češće pojave ovih karcinoma i u znatno mlađem životnom dobu. Dva-tri puta su češći kod muškaraca nego kod žena, a pojava ovih tumora dosad je najčešće povezivana s pušenjem i svakodnevnim konzumiranjem alkoholnih pića. U etiološke faktore ubrajaju se i pojedini virusi, UV zračenje, genetički faktori i drugo [1, 2, 3].

Zbog brzog rasta i sklonosti tumora ka metastaziranju, kao i petogodišnje stope preživljavanja bolesnika s metastazama od svega 34%, OSCK su značajan sociomedicinski problem. Veliki intelektualni napori i materijalna sredstva ulažu se u istraživanja ovih tumora, kako bi se što bolje sagledala njihova priroda, koja će voditi postavljanju precizne dijagnoze, davanju pouzdane prognoze i predviđanju odgovora bolesnika na lečenje. Posebne nade se polažu u istraživanja na polju molekularne biologije, koja se razvijaju u različitim pravcima, od kojih će biti pomenuta prevashodno ona koja se odnose na genetiku i epigenetiku. S aspekta molekularne biologije, neoplastična transformacija je višestepeni proces narušavanja tkivne homeostaze u pravcu nekontrolisane proliferacije ćelija i inhibicije umiranja ćelija apoptozom. Svaki stepen obeležavaju genetičke i epigenetičke izmene, a njihova progresivna akumulacija dovodi do transformacije normalne ćelije u malignu.

GENETIČKA OSNOVA OSCK

Precizna kontrola deobe ćelija ostvaruje se posredstvom gena, čiji proteinski produkti čine složene komunikacione mreže odgovorne za prijem, prenos i konačnu realizaciju mitogenog signala. Ekspanzija klona ili uvećanje ćelijske mase, koje se na kliničkom nivou manifestuje kao neoplazija, uslovljena je strukturnim i funkcionalnim lezijama specifičnih genskih lokusa koji se nazivaju „kancerski geni". Dve ključne grupe gena koji po svojim osobinama zaslužuju ovaj epitet su: a) onkogeni ili mutirani oblici normalnih ćelijskih gena, protoonkogena, koji se nalaze u većini eukariotskih genoma, i b) tumor-supresorski geni – antionkogeni ili inhibitori nekontrolisanog rasta i proliferacije ćelija, a time i malignog fenotipa. Postoje i geni zaduženi za korekciju endogeno, odnosno egzogeno indukovanih lezija naslednog materijala – tzv. DNK reper geni, koji zbog svoje funkcije predstavljaju prvu liniju odbrane integriteta humanog genoma, ali oni neće biti predmet ovoga rada [4-7].

Ćelijska homeostaza se održava zahvaljujući ravnoteži koja postoji u funkcijama ove dve klase gena. S uporednom aktivacijom onkogena i inaktivacijom tumor-supresorskih gena narušava se ta homeostaza i dolazi i do razvoja tumora. Iz ugla sagledavanja mehanizama patogeneze, kao i eventualnih terapijskih intervencija, bitno je ustanoviti u kojem trenutku i koji se gen tokom procesa maligne transformacije aktivirao, odnosno inaktivirao.

Onkogeni

Onkogeni su geni čiji proteinski produkti stimulišu rast, deobu i diferencijaciju ćelija pokretanjem signalnog transdukcionog i transkripcionog regulatornog mehanizma (Slika 1). U obliku protoonkogena (normalni, nemutirani) oni se vremenski i prostorno strogo kontrolisano eksprimiraju. Mutacijom protoonkogeni prelaze u oblik onkogena, koji se nekontrolisano

eksprimiraju. Te mutacije mogu biti: tačkaste mutacije, genske delecije, amplifikacije gena i hromozomski rearanžmani (najčešće translokacije).

Neki od onkogena za koje je dokazana uloga u patogenezi OSCK su *H-ras*, *c-myc* i *c-erbB-2*. Oni su ključni akteri u jednom od centralnih ćelijskih signalizacionih puteva koji vode nekontrolisanoj proliferaciji (Slika 2).

Prema položaju i funkciji, proteinski produkti gena familije *ras* (H, K, N) pripadaju grupi membranskih G-proteina, koji čine prostorno-funkcionalnu vezu između receptora s kojeg primaju mitogeni signal i citoplazmatskih protein-kinaza, na koje ga prenose. Podaci o učestalosti mutacija H-ras u OSCK su veoma šaroliki: od 5% kod stanovnika zapadnih zemalja do 35% kod azijskih naroda. U našoj populaciji učestalost ovih mutacija je 22% [8], s tim da je u podgrupi bolesnika s karcinomom vermiliona usne taj procenat još i veći (55%), a tumači se zajedničkim delovanjem tri faktora rizika: duvana, alkohola i UV zračenja [9]. Smatra se takođe da mutacije u H-ras genu predstavljaju rani događaj u nastanku oralnih tumora i uopšte tumora glave i vrata, jer su zapažene i u određenim prekancerozama [10, 11].

Proteinski produkt gena c-erbB-2 je transmembranski protein koji je takođe uključen u genezu proliferativnog signala od plazma-membrane do jedra. Do onkogene aktivacije c-erbB-2 gena najčešće dolazi usled povećanja broja njegovih kopija, tj. genske amplifikacije, koja za posledicu ima aktivaciju transmembranskog onkoproteina, odnosno iniciranje proliferativnog signala kod izostanka faktora rasta. Aktivacija onkogena c-erbB-2 dovodi do imortalizacije i transformacije ćelija u uslovima *in vitro*, a utvrđena je u mnogim tumorima. U OSCK podaci dobijeni za alteracije u c-erbB-2 genu, u zavisnosti od primenjene metode, kreću se od 20% do 80% [12, 13]. Kod naših bolesnika sa OSCK u 45% slučajeva ustanovljena je mutacija c-erbB-2 gena, i to u 32% amplifikacija, a u 13% delecija [8]. Nasumično povećanje ili smanjenje broja genskih kopija ukazuje na nestabilnost genoma, koji je ključan fenomen u patogenezi tumora [11]. Bez obzira na izvesne oprečne stavove, većina autora ipak smatra da c-erbB-2 gen ostvaruje svoju ulogu u uznapredovalim fazama bolesti.

Ekspresija gena c-myc je takođe promenjena u velikom broju različitih maligniteta. Proteinski produkt ovog gena je jedarni protein koji se vezuje za DNK, koji modulira aktivnost većeg broja gena uključenih u napredovanje ćelije kroz ćelijski ciklus. Stoga kao transkripcioni faktor ostvaruje regulatornu aktivnost u okviru važnih procesa, kao što su stimulacija proliferacije, inhibicija diferencijacije i povećanje osetljivosti na proapoptotske stimuluse [14]. Na osnovu podataka iz literature, ustanovljeno je da c-myc amplifikaciju pokazuje 20-40% oralnih karcinoma kod ljudi u zemljama Evrope i Amerike (što su podaci slični onima dobijenim za našu populaciju), dok je kod stanovnika azijskih zemalja ta vrednost oko 70% [8, 15, 16]. Slično c-erb onkogenu, i c-myc češće mutira (amplifikuje) u tumorima viših histoloških gradusa, kod slabo diferenciranih i tumora s metastazama.

Tumor-supresorski geni

Tumor-supresorski geni (antionkogeni) su geni čiji proteinski produkti inhibiraju neoplastičnu transformaciju, onemogućavajući deobu ćelija ukoliko postoji oštećenje naslednog materijala. Uključeni su u kontrolu ćelijskog ciklusa tako što sprečavaju razvoj ćelije kroz ciklus dok se oštećenja ne poprave, a ako su ona velika, dovode do aktivacije programirane ćelijske smrti (apoptoze). Mutacije u tumor-supresorskim genima izazivaju poremećaje kontrole ćelijskog ciklusa.

Najznačajniji gen iz ove grupe je *TP53*. Održavanje stabilnosti i integriteta ćelijskog genoma je osnovna biološka funkcija ovoga gena i istoimenog proteina. Prema podacima iz literature, protein TP53 je jedan od ključnih transkripcionih faktora ili biomolekula koji svojom regulatornom aktivnošću obuzdavaju deobe ćelija s oštećenim naslednim materijalom (Slika 2). To je istovremeno i gen koji najčešće mutira u većini tumora kod ljudi (gotovo kod 70% solidnih tumora) [17]. Mnoga istraživanja pokazuju da je učestalost mutacija u ovom genu kod kancera glave i vrata oko 60% kod stanovnika Evrope i Amerike, dok je znatno manja kod azijskih naroda, i povezuje se s različitim životnim navikama [18]. Podaci dobijeni za naše bolesnike sa OSCK u potpunoj su saglasnosti s podacima iz literature za zapadne populacije (60%) [8, 19]. Kod naših bolesnika inaktivacija TP53 se usled mutacija povećava s napredovanjem bolesti, pa je tako učestalost mutacija veća kod srednje i slabo diferenciranih tumora (G2 i G3) u odnosu na dobro diferencirane (G1), kao i kod invazivnijih tumora (T3 i T34) u odnosu na manje invazivne (T1 i T2) [20]. U velikom broju radova iz različitih delova sveta takođe je ustanovljena korelacija između zastupljenosti TP53 mutacija i pušenja, ali kod naših ispitanika ta veza nije potvrđena. Sem TP53, sa OSCK se povezuju i promene u drugim tumor-supresorskim genima, kao što su *Rb* i *p16* [21].

VIRUSI I PATOGENEZA OSCK

U poslednje vreme se virusnim infekcijama – naročito infekcijama onkogenim tipovima humanog papiloma virusa (HPV16 i HPV18), čija je uloga u nastanku karcinoma grlića materice odavno poznata – pripisuje poseban značaj i u patogenezi OSCK. Čak se smatra da su HPV-pozitivni i HPV-negativni tumori zapravo potpuno različiti klinički entiteti. Bitan mehanizam delovanja HPV je taj da produkti virusnog genoma, onkoproteini E6 i E7, inaktiviraju ključne tumor-supresorske gene TP53 i Rb, što je signal za nekontrolisanu ćelijsku deobu [21, 22].

Ekstremna procentualna neujednačenost podataka iz svetske literature o značaju HPV-infekcija u patogenezi OSCK navela je istraživače da predlože dva etiopatogenetska mehanizma: HPV+ i HPV-. U karcinomima glave i vrata u kojima su ustanovljeni virusi mutacije u tumor-supresorskim genima (TP53, Rb i dr.) izuzetno su retke, što znači da je gubitak funkcije tumor-supresora posledica interakcije s virusnim onkoproteinima, a ne posledica mutacija u njihovim genima. Zanimljivo je da su podaci čak i na nivou naše populacije oprečni. U jednoj studiji utvrđena je mala učestalost HPV-infekcija kod OSCK u Srbiji i smatra se da je češći HPV put kancerogeneze [8], dok je u drugom istraživanju dobijena visoka učestalost ovih infekcija [23].

ULOGA METILACIJE

Metilacija DNK je epigenetički mehanizam negativne regulacije transkripcije, odnosno genske ekspresije („utišavanje" gena), čiji je značaj u kancerogenezi tek odnedavno sagledan. Ispravan

obrazac metilacije DNK neophodan je preduslov za normalno funkcionisanje ćelije. Narušavanje uobičajenog obrasca metilacije DNK može da izazove promene u važnim ćelijskim mehanizmima, kao što su kontrola ćelijskog ciklusa, DNK reparacija, rezistencija na lekove, apoptoza i angiogeneza. Narušeni obrazac metilacije jeste jedno od obeležja tumorskih ćelija. Veliki broj bolesti čoveka povezan je s aberantnom metilacijom DNK. Najnoviji podaci ukazuju na značaj fenomena globalne metilacije u ranim fazama oralne kancerogeneze, kako kod one koja uključuje HPV infekcije, tako i kod kancerogeneze uzrokovane duvanom i alkoholom, a nezavisne od HPV [24]. U našoj populaciji ispitivana je hipermetilacija nekoliko ključnih tumor-supresorskih gena (p16, DAPK, APC i dr.); zaključak studije je da je aberantna metilacija česta pojava u OSCK [25].

PREDISPOZICIJA ZA RAZVOJ OSCK

„Kancerski geni" i somatske promene u samom tumorskom tkivu predmet su istraživanja brojnih laboratorija već dugo godina. U skorije vreme pažnja se delimično preusmerava i na ispitivanje opšte genetičke konstitucije pojedinaca, u pokušaju nalaženja elemenata koji nekoga čine manje ili više sklonim određenim oboljenjima, uključujući i OSCK. Razlike koje postoje u određenom DNK lokusu između individua jedne vrste označene su kao DNK polimorfizmi i oni obuhvataju polimorfizme nukleotidne sekvence i polimorfizme dužine sekvence. Polimorfizmi nukleotidne sekvence mogu biti vezani za varijabilnost tipa bazne zamene, a to su tačkasti polimorfizmi (SNP) ili polimorfizmi vezani za inserciju ili deleciju određenog niza nukleotida. Funkcionalni polimorfizmi utiču na ekspresiju gena u kojima se nalaze, pa se očekuje da će se odraziti i na funkciju datog proteina (enzima) odnosno procese u koje su ti enzimi uključeni. Studije asocijacije se koriste u proceni stepena povezanosti genskih polimorfizama s pojavom određene bolesti. Ove analize se zasnivaju na poređenju učestalosti datog polimorfizma kod obolelih osoba s učestalošću odgovarajućeg polimorfizma u populaciji zdravih. Neki polimorfizmi su se pokazali kao korisni pokazatelji u određivanju rizika za razvoj bolesti, njen tok i odgovor na lečenje.

Pored polimorfizama, koji su opšteprihvaćeni modulatori rizika u kancerogenezi, kao što su funkcionalni polimorfizmi u genima koji kontrolišu proliferaciju i smrt ćelija, DNK reparacioni mehanizmi i dr., sa stanovišta uloge potencijalnog markera susceptibilnosti za razvoj OSCK interesantni su i polimorfizmi u genima odgovornim za inflamatorne reakcije (geni za citokine), za metabolizam ksenobiotika, odnosno detoksikaciju (geni za glutation-transferaze) i slični [26-29].

NAPOMENA

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