STUDY OF ABCB1 MULTIDRUG RESISTANCE PROTEIN IN A COMMON OROFACIAL MALFORMATION

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The onset of embryonic malformations is greatly determined by the intrauterine environment, conditioned by maternal lifestyle, diet, drugs and medication intake, in addition to both foetal and maternal genotypes. Maternal C677T MTHFR genotype has been identified as important factor in cleft lip with or without cleft palate (CL/P) etiology. In the present study we evaluated the possible interaction between maternal methylenetetrahydrofolate reductase (MTHFR) and foetal ABCB1 genotypes. ABCB1 gene codes for a drug-transport pump in charge to protect the cell by extruding a variety of harmful exogens, but with a reduced activity in a folate-restricted condition. Maternal 677T genotype is translated in a reduced folate availability for the developing embryo who consequently may becomes more exposed to external insults. A family based association analysis was performed to test the effect of ABCB1 polymorphisms in clefting, in the whole sample and in the stratified sample accordingly to maternal MTHFR genotype. No evidence of association between ABCB1 polymorphisms and CL/P was detected. This suggests that ABCB1 or ABCB1-MTHFR feto-maternal interaction could have no effect in orofacial clefting or could play a role in a limited number of cases.

EVIDENCE OF AN INVOLVEMENT OF TFAP2A GENE IN NONSYNDROMIC CLEFT LIP WITH OR WITHOUT CLEFT PALATE: AN ITALIAN STUDY

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Unraveling of factors involved in multifactorial diseases is a great challenge. Different approaches can be contemplated and applied to a variety of congenital malformations. In the present investigation TFAP2A has been considered a good candidate gene for nonsyndromic cleft lip with or without cleft palate (NSCLP) etiology, basing on a sum of considerations. TFAP2A has been seen involved in orofacial development in mice; it is located in the NSCLP candidate region 6p24; it codes for a transcription factor which regulates expression of IRF6, a gene implied in NSCLP; finally, it is embroiled in the branchiooculofacial syndrome, that includes clefting as feature. A family based association analysis was performed with a sample study of 405 NSCLP triads. Evidence of association was obtained with both single marker and haplotype analyses, thus providing a support for TFAP2A in NSCLP etiology.
NO ASSOCIATION BETWEEN POLYMORPHISMS IN CUBILIN, A GENE OF THE HOMOCYSTEINE METABOLISM AND THE RISK OF NON-SYNDROMIC CLEFT LIP WITH OR WITHOUT CLEFT PALATE

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Epidemiological studies have correlated lower maternal periconceptional levels of plasma folate and cobalamin with increased risk of delivering offspring presenting congenital malformations such as cleft lip with or without cleft palate (CL/P) or neural tube defects. A number of genetic studies aimed at correlating these biochemical levels or the occurrence of malformations with specific genetic defects or polymorphisms have been successfully performed. The cubilin gene (CUBN) codes for a carrier that plays a crucial role in cobalamin cell internalization. CUBN polymorphisms were previously found to be associated with spina bifida occurrence. In this work, a family-based association study was performed to test CUBN involvement in CL/P. A sample of 391 CL/P triads was investigated with three single nucleotide polymorphisms mapping on the cubilin gene. Association tests indicated no significant association between CL/P and marker alleles or marker haplotypes. No evidence of maternal effect and imprinting were obtained. These data suggest that CUBN is not involved in CL/P onset in the investigated Italian population.

EVIDENCE OF LEF1 FETAL-MATERNAL INTERACTION IN CLEFT LIP WITH OR WITHOUT CLEFT PALATE IN A CONSISTENT ITALIAN SAMPLE STUDY

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Epithelial mesenchymal transformation is considered a cardinal process in orofacial development. Several molecular players appear to be involved in this delicate mechanism: the activation of LEF1 transcription factor by transforming growth factor beta 3 seems to be a key step for the correct flow of events. The failure of orofacial processes during embryonic development may provoke cleft lip and/or cleft palate malformations. The scope of the present investigation was to verify whether genetic variants at LEF1 could influence the risk of orofacial clefting. The approach was a family based association study involving a total of 512 Italian patients and their parents, 401 having cleft lip with or without cleft palate (CL/P) and 111 with cleft palate only (CPO). Haplotype association analysis provided moderate evidence of an association with clefting (p 0.01). A log-linear likelihood-based method was used to verify maternal and foetal-maternal association. An association between the maternal genotype and the occurrence of CL/P was observed at two polymorphic loci, at rs10022956 (P = 0.0049) and rs10025431 (P = 0.0065) respectively, while a foetal-maternal effect modulating the risk of clefting was found at locus rs10025431 (P = 0.0071). These data further corroborate the importance of the mother’s genotype with regard to susceptibility to malformations and early-onset diseases.
STUDY OF THE 12q13 REGION IN NONSYNDROMIC CLEFT LIP WITH OR WITHOUT CLEFT PALATE

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The 12q13 region has been suggested as a candidate locus for orofacial cleft by different investigators. In the present study we tested the region for linkage with non syndromic cleft lip with or without cleft palate in a collection of 39 Italian multigenerational families, using microsatellite markers. No evidence of linkage was detected between the marker map and NSCLP under different mode of inheritance nor with a nonparametric method. Formal level of linkage exclusion, were obtained for each point of the map. Genetic heterogeneity and the different impact of the candidate locus among populations could explain conflicting results obtained in different studies.
Bone tissue is a three-component porous material composed principally of organic matrix (mainly collagen), mineral, and water: changes in the proportions of these components will alter the material properties (1). Small adjustments in mineral content can significantly affect the mechanical properties of bone (2). Furthermore, in bone tissue, the distribution of the mineral depends on the rate of the bone turnover. A high turnover rate results in a large difference in mineral content between the interstitial bone and the surface layer. So, increasing mineralization density increases the strain resistance of bone (3).

However, the presence of collagen in the bone matrix is crucial to determine the quantity of energy required to produce matrix failure (4). The mechanical loading is an important determinant of collagen fiber orientation, and it could alter osteoblasts in a manner that causes a characteristic orientation in the fibers they synthesize (5). Therefore, determining the orientation of collagen fibers in human bone tissues is indispensable when studying the relationship between the physical properties and the structure (6).

According to classical histology, bone tissue may be

HISTOMORPHIC-METRIC EVALUATION OF AN IMPLANT RETRIEVED FROM HUMAN MAXILLA AFTER 13 YEARS

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Fixture fracture is the most catastrophic failure of implant components because it usually causes the loss of the implant. Nevertheless, the osseointegrated fractured implants represent a very useful opportunity to study in humans the effects of loading to the peri-implant bone microstructure. The aim of the present study was to evaluate the interplay between microstructure and function of the bone around an implant retrieved from human maxilla after 13 years. There was 1 fractured Dental Implant Line (sand blasted surface from a patient placed in the anterior region of the maxillary bone (2.1) after a bone augmentation procedure, and it was processed for histology. The specimen was analyzed under the scanning electron microscope (SEM), the confocal scanning laser microscope (CSLM) and brightfield light microscope (LM) equipped with circularly polarized light (CPL). The BIC rate of the implant retrieved after 13 years was (mean ±SD) 68.7 ± 3.7. The crestal bone down the implant platform damage appeared to be under modeling process. The transverse collagen fiber orientation (CFO) (mean ±SD) under the lower flank of the threads was 20.4 ± 3.5 x 10⁴ pixel while the longitudinal CFO was 19.8 ± 2.8 x 10⁴ pixel (P>.05). In the inter-threads region the transverse CFO (mean ±SD) was 15.0 ± 4.0 x 10⁴ pixel while the longitudinal CFO was 21.4 ± 3.0 x 10⁴ pixel (P>.05). The osteocytes numbers (mean ±SD) was 130 ± 34. Under SEM with back scattered electrons (BSE) signal the peri-implant bone appears mainly lamellar and highly mature with several osteons organized in the implant inter-threads areas. The fracture of the implant was most probably correlated to a fatigue of the material mainly associated to a damage of the internal coil. Surprisingly, it was noted a lack of implant site-specific CFO of the bone extracellular matrix facing the threaded dental implant notwithstanding the high level of BIC rate.

Key Words: Circularly Polarized Light Microscopy, collagen fiber orientation, bone implant contact rate, implant fracture, Dental Implant Line
The main factor in determining the mechanical properties of bone is the collagen configuration in the matrix and corresponding orientation of mineral crystallites (1). According to classical histology, bone tissue may be classified in relation to the spatial orientation of collagen fibers. Two different types of bone have been recognized: oven-fibered bone and parallel-fibered bone (lamellar or non-lamellar) (2). Woven bone has been estimated to contain four to eight times more osteocytes than lamellar bone (3). Osteocytes plays a crucial role in maintaining the mechanical quality of bone, and osteocyte density could be considered as an alternative index in assessing bone quality (4). The coefficient of variation of osteocyte lacunar density (number osteocyte lacunae per bone area) increases linearly with age, and aging bone tissue is characterized by increased heterogeneity in the spatial organization (numbers) of osteocytes (5). So, the bone mass is determined by the control of osteocyte number (6).

It is known that static loads have no effects on bone mass; however, experimental information makes it plausible that amplitude, rate, frequency and duration of loading are all important for bone metabolism (7). The osteocytes, through their network, provide a stimulus to HISTOMORPHIC-METRIC EV ALUATION OF AN IMMEDIATELY LOADED IMPLANT RETRIEVED FROM HUMAN MANDIBLE AFTER 2 YEARS

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The aim of the present study was to evaluate the interplay between microstructure and function of the bone around an immediately loaded implant retrieved from human maxilla after 23 months due to fracture. A spiral implant of 3.3 mm x 15 mm was placed in a male 53 years old in the anterior region of the mandible bone (4.1) and it was processed for histology. The specimen was analyzed under the confocal scanning laser microscope (CSLM) and brightfield light microscope (LM) equipped with circularly polarized light (CPL). The BIC rate was 76.7± 4.9 (mean ±SD). Many cement lines indicates an high remodeling rate of the bone. The transverse collagen fiber orientation (CFO) (mean ±SD) under the lower flank of the thread near the tread tip was 55.2 ± 4.8 x 10⁴ pixel while the longitudinal CFO was 45.8 ± 2.3 x 10⁴ pixel (P<.05). In the inter-threads region the transverse CFO (mean ±SD) was 36.4 ± 2.4 x 10⁴ pixel while the longitudinal CFO was 65.6 ± 6.5 x 10⁴pixel (P<.05). The osteocytes numbers (mean ±SD) was 205 ± 45 in the peri-implant bone and 144 ± 53 in the native bone (P=.007). After 2-years of loading the SLA spiral implant was well osseointegrated but still surrounded by woven bone. The osteocytes density was significantly higher in the peri-implant bone than in the native bone. The transverse collagen fibers were significantly associated with the lower flank of the implant threads, while the longitudinal collagen fibers were more represented in the straight surface of the implant. The implant fracture was correlated to crestal bone resorbing and subsequent fatigue yielding.
Formalin fixation under conditions that adversely affected the quality of the DNA, or indeterminant assay, or extensive tumor necrosis can compromise the genetic analysis of a brain biotic sample. The success of DNA extraction and Methyl Guanine Methyl Transferase (MGMT) promoter methylation testing could be improved by freezing of fresh tumor tissue at the moment of biopsy. To ensure an increased concentration of the DNA samples the withdrawal should be performed in an area with high probability of neoplastic cells. From May 2007 to January 2011 fifty-two frameless neuronavigation brain needle biopsy were performed at the Neurosurgery Unit of the “Arcispedale Santa Maria Nuova” City Hospital of Reggio Emilia. The “image-guided” neuronavigated protocol sampling provided withdrawal specimens highly correlated with neuroimaging characteristics of the lesions. In this study the Authors report the genetic analysis on 24 cases of freezing fresh tissue from brain needle biotic sample starting from July 2008. The molecular determination of MGMT promoter was assessed with the Nested-Methylation Specific-Polymerase Chain Reaction on fresh or cryopreserved needle biotic tissue. The genetic characterization was feasible in all the biotic samples. The MGMT promoter was methylated in eleven patients, including a brain infection. The diagnostic yield of brain biopsy could be increased by the neuronavigated trajectories and the intraoperative frozen sections. In the future the availability of the molecular-genetic characterization of a brain tumor before open surgery will provide important information for the optimal treatment. The MGMT promoter status analysis on needle biotic fresh tissue could be available also for that patient not eligible for surgical remotion of the tumor.
Presently, there are limited treatment options for glioma; glioblastoma, the most common glioma subtype, remains an incurable disease with a median survival of 15 months, even with radiation and temozolomide therapy (1). A patient may not be entered in recent chemotherapy protocols without a histopathological or molecular genetic analysis (2).

The most widely studied epigenetic mark is DNA methylation that occurs at cytosine residues in the context of CpG dinucleotides. The O6-methylguanine DNA methyltransferase (MGMT) promoter methylation has recently been recognized as the most powerful determinant of chemotherapy sensitivity in patients with glioblastomas (3).

Since 2008, sequencing of gliomas has identified mutations in the isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) genes. Patients with IDH1 mutated glioblastoma multiforme have a better prognosis than those without IDH1 mutations, with respect to both overall survival (OS) and progression-free survival (4, 5). IDH1 appears to have a native function as a tumor suppressor that, when mutational inactivated, contributes to the malignant phenotype of gliomas.

DETECTION OF IDH1 MUTATIONS AND THE STATUS OF MGMT PROMOTER ON INTRAOPERATIVE FRESH TISSUE SECTION FROM FRAMELESS NEURONAVIGATION NEEDLE BIOPSY. ANALYSIS ON 17 PATIENTS WITH BRAIN GLIAL TUMOR INELIGIBLE FOR CRANIOTOMY AND TUMOR RESECTION

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It is well known that primary and secondary glioblastomas are histologically largely indistinguishable. Therefore, the detection of IDH1 mutations or the status of the MGMT promoter on a simple bioptic sample could be one of major diagnostic and prognostic importance for glial patients that complements clinical criteria for distinguishing secondary from primary glioblastomas and to predict a more favorable prognosis. Currently, biopsy is the method of choice to obtain tissue from intracranial lesions with uncertain neurodiagnostic findings or in deep locations, with a minimal invasive approach. The needle biopsy with frameless neuronavigation could provide a sampling with elevated diagnostic yield and high concentration of DNA, due to the “image-guided” computer assisted technique of needle insertion through the most neurodiagnostic representative tumoral area. The freezing of fresh tumor tissue at biopsy could greatly improve the success of DNA extraction. The concentration of the DNA samples can also improved from a withdrawal in an area with high probability of neoplastic cells. The present study reports the results of 17 patients who had undergone frameless image-guided intracranial needle biopsy from April 2008 until July 2010 at Neurosurgery Unit of the “Arcispedale Santa Maria Nuova” of Reggio Emilia. For these patients the molecular determination of MGMT promoter was assessed with the Nested-Methylation Specific-Polymerase Chain Reaction and the screening of mutations in IDH1 e IDH2 genes was performer by polymerase chain reaction (PCR) and direct sequencing on fresh or cryopreserved needle bioptic tissue.
DETECTION OF IDH1 MUTATIONS AND THE STATUS OF MGMT PROMOTER ON INTRAOPERATIVE FRESH TISSUE SECTION FROM FRAMELESS NEURONAVIGATION NEEDLE BIOPSY. ANALYSIS ON 17 PATIENTS WITH BRAIN GLIAL TUMOR INELIGIBLE FOR CRANIOTOMY AND TUMOR RESECTION

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Calcium sulfate (CaS) is a highly biocompatible material and enhances bone formation in vivo. However, how CaS alters osteoblast activity to promote bone formation is poorly understood. To study how CaS can induce osteoblast differentiation in mesenchymal stem cells, the expression levels of bone related genes and mesenchymal stem cells marker were compared in normal osteoblasts and dental pulp stem cells, using real time Reverse Transcription-Polymerase Chain Reaction. Gene differentially expressed between the two cells type were the transcriptional factor RUNX2, osteopontin (SPP1), COL1A1 (collagen type 1α1) and alkaline phosphatase (ALPL). The obtained results demonstrated that CaS strongly influences the behavior of DPSCs in vitro enhancing proliferation, differentiation and deposition of matrix.

POLYLACTIDE-POLYGLYCOLIDE RESORBABLE PLATES STIMULATES ADIPOSE TISSUE-DERIVED STEM CELLS TOWARDS OSTEOBLASTS DIFFERENTIATION

Polylactide, polyglycolide materials or devices have been utilized routinely during maxillofacial, craniofacial, and orthopaedic reconstructive surgical procedures.(1) These materials combine the benefits of rigid fixation with the advantages of biodegradation, avoiding the need for implant removal and minimizing the risk of other complications.(2) To study how polylactide, polyglycolic acid plates (PLPG plates) can induce osteoblast differentiation and proliferation in mesenchymal stem cells, the expression levels of bone related genes (RUNX2, SP7, ALPL, SPP1, COL1A1, COL3A1 and FOSL1) and mesenchymal stem cells marker (ENG) were measured in adipose derived stem cells (ADSCs) and normal osteoblast (NO) cultivated on PLPG plates after 15 and 30 days of treatment using real time Reverse Transcription-Polymerase Chain Reaction. Significantly differentially expressed genes among ADSCs and NO were SP7, ENG, FOSL1, RUNX, ALPL and SPP1 in the first 15 days of treatment and SP7, ENG FOSL1, COL3A1 COL1A1, SPP1 and ALPL after 30 days. The present study demonstrated that PLPG plates strongly influences the behavior of ADSCs in vitro by enhancing proliferation, differentiation and deposition of matrix.
ASSESSMENT OF PAIN ASSOCIATED WITH INSERTION TORQUE OF DENTAL IMPLANTS. A PROSPECTIVE, RANDOMIZED-CONTROLLED STUDY

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This study investigated pain experience following dental implant placement in relation to insertion torque using questionnaires. A total 80 implants were placed in 20 patients. Each patient received 4 implants at different times. One implant was inserted and, then, after 40 days was placed the second implant, after 80 days was placed the third implant and after 120 days was placed the fourth implant. At each time the peri-implant bone levels were evaluated on intraoral radiographs taken with the paralleling technique. The implants were placed with a dynamometric key at 35N, 50N, 65N, 85N. Patients were asked to evaluate their pain experience during surgery, 24 hours after surgery, and at 2 days, 4 days, 1, 2, and 4 weeks after surgery on special pain assessment forms. A separate form was used for each time point. Pain was assessed using a descriptive numerical rating scale of 0 to 10, with 0 indicative of no pain and 10 representing the worst pain imaginable. Patients were instructed that a score of 1 to 3 was indicative of mild pain, 4 to 6 was indicative of moderate pain, and 7 to 10 was indicative of severe pain. A significant correlation pain scores and insertion torque was found between group III and group IV vs group II and group I during surgery, at 24 hours, 2 days, 4 days, 1 week, 2 weeks p≤ 0.05. No statistical difference was found between group I vs. group II during surgery, at 24 hours, 2 days, 4 days, 1 week, 2 weeks p≥ 0.05. In conclusion, elevated insertion torque values produces pain and resorption of the crestal bone around the implants.

EXPANSION OF THE ALVEOLAR BONE CREST WITH ULTRASONIC SURGERY DEVICE: CLINICAL STUDY IN MANDIBLE

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The purpose of this paper was to document the application to the split-crest mandibular procedure in two stage in order to avoid cortical resorption due to periosteal detachment in buccal cortical bone of the alveolar crest. Twenty-two healthy patients with non-contributory past medical history (14 women and 8 men, all non-smokers, mean age 59 years, range 54–65 years) were included in this study. After buccal mucoperiosteal flap was followed by a sagittal corticotomy in the coronal area of the alveolar crest and a second sagittal corticotomy, but in a lower (basal) position and two vertical corticotomies in the buccal wall, using a ultrasonic surgery device (Surgysonic, Esacrom, Imola Italy). Adequate crest expansion was achieved without compromising cortical vascularisation by utilising a combination of scalpel, thin chisels and threaded osteotomes (Bone System, Milano, Italy). Postoperative results were assessed by panoramic and periapical radiographs. Ossification of the osteotomy lines was evident and could be observed as sites with increasing radiopacity on panoramic and periapical radiographs 3 months after implants insertion. No dehiscence of the mucosa was observed. No patient suffered from hypoesthesia. The mean horizontal bone increase in coronal area was 5±3 mm. Mandibular ridge expansion using a split-crest technique that included grafting the implant sites with a ultrasonic surgery device is a viable therapeutic alternative for implant placement in this patient population.
ANALYSIS AND STRUCTURAL EXAMINATION OF SCREW LOOSENING IN ORAL IMPLANTS

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Biological and technical failures of implants have already been reported. Mechanical factors are certainly of importance in implant failures, even if their exact nature has not yet been established. The abutment screw fracture or loosening represents a rare, but quite unpleasant failure. The aim of the present research is an analysis and structural examination of screw thread or abutment. In this study broken screws were excluded. A total of 58 screw thread loosening were observed, 5 Branemark, (Nobel Biocare, Gothenburg, Sweden) 4 Implant Innovation (Riverside Drive Palm Beach Gardens, FL, USA) and 7 Restore (Lifecore Biomedical, Chaska, Minnesota, USA) and 42 T.B.R. implant (Benax, Ancona, Italy). The loosened abutment screws were retrieved and analyzed under SEM. Many alterations and deformations were present in concavities and convexities of screw threads.

INCIDENCE OF LOW RISK HUMAN PAPILLOMAVIRUS IN ORAL CANCER: A REAL TIME PCR STUDY ON 278 PATIENTS

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Squamous cell carcinoma is the most frequent malignant tumour of the oral cavity. It is widely known that tobacco and alcohol consumption are the major causes of the development of oral squamous cell carcinoma (OSCC). The human papilloma virus infection has also been postulated as a risk factor for squamous cell carcinoma, although conflicting results have been reported. The aim of this study is to evaluate the presence of high-risk and low-risk type human papillomavirus in a large sample of squamous cell carcinoma limited to the oral cavity by means of quantitative real-time polymerase chain reaction. Data were obtained from 278 squamous cell carcinoma limited to oral cavity proper. Sequencing revealed that 5 samples were positive for HPV type 16, 5 for HPV type 11, and 1 for HPV type 6. Human papillomavirus 11 was detected in 5 tumours out of the 278 examined. The prevalence rate for Human papillomavirus 11 was 1.8% (C.I. 0.7-3.9). The matched case-controls analysis indicated that the prevalence among controls did not significantly differ with respect to cases and that Human papillomavirus 11 alone did not correlate with squamous cell carcinoma.
Squamous cell carcinoma (SCC) of the head and neck is a major health problem worldwide, accounting for over 300,000 cases annually (1). Among different head and neck oncological sites (i.e. oral cavity, pharynx, larynx and paranasal sinuses), SCC limited to the oral cavity in its strictest definition (i.e. in front of the tonsils) accounts for the vast majority of cases (1).

The behavior of head and neck SCC depends on several variables (2). Metastases, which occur via the lymphatic system, are the main cause of death; their incidence is significantly correlated to the localization and clinical stage of the primary tumor, as well as the degree of deep infiltration and cell differentiation (3).

Progression from normal mucosa to premalignant lesions or invasive cancer is a multistep process that includes the accumulation of a number of discrete genetic alterations, such as the activation of oncogenes and the inactivation of tumor suppressor genes. Recognized risk factors for SCC, such as tobacco and alcohol consumption, act in this progression by increasing the DNA damage rate (3). Viruses and other microbes have been intensively investigated as it had been suggested that they were involved in oral SCC (7).

The discovery of markers with prognostic predictive values would represent great advances in clinical practice. Several investigations have been performed to identify genetic markers which can predict progression from oral dysplasia to oral cancer while markers of tumor stage progression have been less intensively studied (4). A number of frequent genetic alteration have been identified, however, data are still insufficient to transfer this knowledge to clinical practice. The most common losses have been observed in chromosome regions 1p, 3p, 4p, 5q, 8p, 9p, 10p, 11q, 13q, 17p, and 18q; while gains have frequently been observed at 1q, 3q, 5p, 7q, 8q, 9q, 11q, 12p, 14q, and 15q (11).

Recently, members of our group have identified new potential markers for tumor progression that are less LOH AT PDCD4, CTNNB1, AND CASP4 LOCI CONTRIBUTES TO STAGE PROGRESSION OF ORAL CANCER

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Squamous cell carcinoma is the most frequent malignant tumor of the oral cavity. Markers of tumor progression that could help to define diagnosis, plan treatment and implement prognosis have still to be identified. Seven candidate markers for tumor progression were investigated using a loss of heterozygosity (LOH) assay. The sample was made up of 51 squamous cell carcinoma and adjacent normal tissues from the same patients. LOH at one, or more, markers was a relatively frequent event that was observed in 53% of tumors. The number of losses detected in each tumor was significantly associated with tumor severity. Significant association between UICC stage grouping and LOH was found for 3 gene loci: programmed cell death 4 (PDCD4), catenin beta 1 (CTNNB1), and caspase 4 (CASP4). No association between allelic loss and the occurrence of lymph node metastasis was found for any of the seven investigated loci. Overall, LOH contributes to tumor progression of oral SCC. A specific role for PDCD4, CTNNB1, and CASP4 was found.
Oral Squamous Cell Carcinoma (OSCC) is the sixth most common cancer and accounts for approximately 5% of all malignant tumors worldwide and a subgroup of OSCC have been demonstrated to contain anogenital HPV infection. The high risk HPV type 16 tends to be the most predominant type detected in oral cancer (1).

DOUBLE DEMONSTRATION OF ONCOGENIC HIGH RISK HUMAN PAPILLOMA VIRUS DNA AND HPV-E7 PROTEIN IN ORAL CANCERS

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Oncogenic HPVs are necessarily involved in cervical cancer but their role in oral carcinogenesis is debated. To detect HPV in oral cancer, 38 cases of formalin fixed-paraffin embedded OSCC were studied by both DNA genotyping (MY09/11 L1 consensus primers in combination with GP5-GP6 primer pair followed by sequencing) and immunohistochemistry (monoclonal Abs against capsid protein and HPV-E7 protein, K1H8 DAKO and clone 8C9 INVITROGEN, respectively). HPV-16 tonsil cancer was used as positive control. The overall prevalence of HPV infection in OSCCs was 10.5%. Amplification of DNA samples showed single HPV DNA infection in 3 cases (HPV16; HPV53; HPV70) and double infection in one case of cheek cancer (HPV31/HPV44). The overall HR-HPV prevalence was 7.5%. E-7 antigen was immunohistochemically detected in all HPV-positive cases. HPV+ OSCC cases showed an overall better outcome than HPV negative oral cancers, as evaluated by Kaplan-Meier curves. HPVs exert their oncogenic role after DNA integration, gene expression of E5, E6 and E7 loci and p53/pRb host proteins suppression. This study showed that HPV-E7 protein inactivating pRb is expressed in oral cancer cells infected by oncogenic HPV other than classical HR-HPV-16/18. Interestingly HPV-70, considered a low risk virus with no definite collocation in oncogenic type category, gives rise to the expression of HPV-E7 protein and inactivate pRb in oral cancer. HPV-70, as proved in current literature, is able to inactivates also p53 protein, promoting cell immortalization. HPV-53, classified as a possible high risk virus, expresses E7 protein in OSCC, contributing to oral carcinogenesis. We have identified among OSCCs, a subgroup characterized by HPV infection (10.5%). Finally, we have proved the oncogenic potential of some HPV virus types, not well known in literature.
Autoimmune subepidermal blistering disorders are a large family of skin/mucous diseases including, among others, mucous membrane pemphigoid (MMP) (previous named cicatricial pemphigoid) (1). In vivo linear deposition of immune deposits (immunoglobulins, complement or both) along the basement membrane zone (BMZ) was the common feature that characterize pemphigoid (2). However, while bullous pemphigoid (BP) generally affect the skin and have only minor oral involvement, MMP mainly involves the mucous membranes, most frequently the oral and ocular mucosa (3).

Among the classical cadherins, E- (epithelial) and P- (placental) cadherins are involved in the selective adhesion of epidermal cells. E-cadherin is expressed on the cell surfaces of all epidermal layers, whereas P-cadherin is expressed only on the surfaces of the basal and most immediate suprabasal cells of the epidermis (4-6). To the best of our knowledge, the expression of E- and P-cadherin in MMP lesions has not previously been reported. Thus, to gain insight into the role of cadherins on the acantholysis of keratinocytes and further investigate the pathogenesis of Mucous Membrane Pemphigoid, we examined the expression of P-cadherin and E-cadherin, in normal human oral mucosa, lesional and peri-lesional mucosa in MMP. Twenty-nine samples from paraffin-embedded specimens of MMP were used for the study. Five specimens of healthy oral mucosa were evaluated as control group. To evaluate the E- and P-Cadherin expression, a mean percentage of positive cells was determined from the percentage of positive cells derived from the analysis of 100 cells in ten random areas at x400 magnification. It was observed that E-cadherin was weakly and discontinuously expressed on the epithelial layers of pemphigoid mucosa, while it was intensively expressed on all keratinocytes in normal human skin. In contrast, P-cadherin was strongly expressed throughout the entire epidermal layer in MMP samples, although its expression is restricted to the basal cell layer in normal human skin. Statistical analyses showed that the percentage of E-cadherin positive cells in the epithelium of pemphigoid cases was significantly decreased compared with that in normal human mucosa. There was a significant increase in the percentage of P-cadherin positive cells in the epithelial layers of MMP compared with normal human mucosa. The present study showed that there is downregulation of E-cadherin expression and upregulation of P-cadherin expression in MMP mucosa, which may be involved in the pathogenesis of MMP.
Intercellular adhesiveness is mediated by a family of glyco-proteins named cadherins (1), which are composed of an extra-cellular domain, involved in Ca++-dependent homophilic binding to adjacent cells, a trans-membrane domain, and an intra-cellular domain which binds to proteins called catenins (2). Binding of cadherins to α-catenin, a protein homologous to vinculin which binds to actin, and, hence, the formation of the zonula adherens, is mediated by β- or γ-catenin, which act as adaptors between cadherins and α-catenin. Therefore, these catenins play a crucial role in cadherin function and were recently shown to be involved in other functions such as signaling and activation of transcription factors and cell motility (3). Moreover, in the Wnt/β-catenin pathway the stabilization and reduced degradation of β-catenin lead to control expression of genes that regulate a diverse array of biological processes. Wnt are cysteine-rich secreted glycoproteins, identified in organisms ranging from hydra to humans (4), that through the interaction with their ligands can activate several different receptor-mediated

**EXPRESSION OF β-CATENIN AND γ-CATENIN IN MAXILLARY BONE REGENERATION**

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β- and γ-catenin are components of catenin family involved in cadherin adhesion function. Recently it has been shown that this family is involved in other functions such as signaling and activation of transcription factors. The final goal of this study was to evaluate the role of β- and γ-catenin in bone cell physiology and bone regeneration. Formalin-fixed-paraffin embedded specimens of 15 human bone specimens after sinus lift were collected and examined by immunohistochemistry using primary antibodies against β- and γ-catenin. Staining intensity and cellular localization were evaluated. β and γ-catenin showed a very high level of expression in human bone tissues. In particular, catenins were expressed in cells with morphological findings of osteoblasts in the areas of new bone formation at the junction between mineralized and unmineralized tissue, between osteoid matrix and bone. Osteoclasts showed also positivity for catenins. Osteocytes, cells located in lacunae of mature mineralized bone with function of bone vitality maintenance, showed no expression for catenins. Specimens characterized by high amount of catenins in osteoblasts at 1\(^{st}\) month showed high grade of bone maturation at 3\(^{rd}\) month. Data demonstrated an overall involvement of catenins in human bone tissues and in particular during bone regeneration process. The presence of staining for β- and γ-catenin particularly in osteoblasts demonstrates a significant role of catenins in functions, other than in cadherin interaction, such as signaling and activation of transcription factors during differentiation of bone tissues.
The presence of inflammatory reaction in peri-tumoural connective tissue is generally considered as a defense mechanism against cancer, but inflammation tissue in malignant transformation and early steps of oncogenesis has been recently proven to play a supporting and aggravating role in some carcinomas. Aims of this retrospective study were to evaluate in OSCCs the independent association of peri-tumoral inflammatory infiltrate (PTI) with local recurrence (LR) or survival outcome, and to verify whether PTI can be considered a marker of prognosis. Data from 211 cases of OSCC, only surgically treated between 1990 and 2000, were collected and retrospectively analyzed for PTI and the event LR (5 yrs follow-up at least) by means of univariate-multivariate and neural networks analyses. Patients (mean age 65.3 ± 12.4 yrs, M/F = 2.98) showed presence of PTI in 68.2% (144/211): (+) in 27.0%, (+++) in 15.6%; PTI was found reduced in 24.7% of cases and absent in 7.1%. In overall PTI+ve group (n=144), 66 were TNM Stage I, 33 Stage II, 45 Stage III, none Stage IV. LR (mean 6 ± 4 months) was present in 87/211 (41.2%) patients, of which 43/144 (29.8%) in OSCCs with PTI [23 (+), 13 (++) and 7 (+++) vs. 44/67 (65.7%) in OSCC with PTI -/+ or PTI–ve ones. By univariate analysis, PTI+ve cases showed a significant lower risk to have LR (p<0.0001; OR= 0.2297; CI= 0.1277:0.4134) vs PTI -/+ or –ve ones, especially among cases with higher PTI value (+++) (OR= 0.1718; CI= 0.0749:0.3939). Multivariate analyses (Logit model and neural networks) confirmed the same datum: presence of PTI was an independent predictive variable accounting for a better tumoural outcome without LR (Logit and neural networks values: OR’ 0.226; CI= 0.113:0.454; ROC Area = 0.66, respectively). In terms of prognostic significance, elevated PTI was found to have an independent association with the poorest overall survival rate (P = 0.056). Our findings strongly suggest the importance to investigate routinely PTI in OSCCs, as useful marker of tumoral behavior and prognosis, and warrant further studies on its specific cellular nature.
Oral Squamous Cell Carcinoma (OSCC) is the most common cancer of the oral cavity and it is the 6th most common malignancy with more than 275,000 new cases and 127,000 deaths worldwide in 2002 (1). Despite oral cavity is a readily accessible region for visual examination and cancer risk factors are well-known, a significant amount of OSCCs are still diagnosed late (Stage III or IV), reducing the 5-year survival rate and worsening morbidity and mortality related to the disease (2). Furthermore, OSCC is believed to arise from Oral Potentially Malignant Disorders (OPMDs) in the 50% of cases, coming from hyperplasia, mild, moderate, and severe dysplasia to carcinoma in situ, and finally invasive OSCC from stages I to IV (3).

Conventional Oral Examination (COE) using incandescent white light (WL) is still the most widely used approach for OSCC and OPMD diagnosis and follow-up. The criteria used in COE for suspicion of an oral neoplastic lesion are based on size, shape, color, and consistency of the lesion, as well as on the presence of pain, bleeding, and ulceration. However, COE is a subjective and operator-dependent technique, and it may miss early lesions or false-positive results may occur due to the subjective nature of the diagnosis.

Direct visualization of the oral tissue autofluorescence has been recently reviewed in several studies as a possible adjunctive tool for early recognition and diagnosis of potentially malignant and malignant oral disorders. The aims of this study were to assess: a) the value of a simple handheld device for tissue auto-fluorescence visualization of potentially malignant oral lesions; and b) the sensitivity, specificity and diagnostic accuracy of tested device, using histological examination as the gold standard. 175 consecutive patients, with at least one clinical oral lesion, were enrolled in the study. Clinical conventional inspections were performed for each patient by two blind operators. Then, oral biopsy and histological examination were performed. Pathologist was blind with respect to the autofluorescence results. The 175 histological assessments revealed no dysplasia, mild dysplasia, moderate/severe dysplasia and OSCC, in the 67.4%, 8.6%, 8%, 16% of cases, respectively. Oral lesions diagnosed as OSCC were found as positive under fluorescent light in the 96.4% of cases. Statistically significant correlation was observed between oral dysplastic lesions and the loss of tissue fluorescence (p-value=0.001). Low sensitivity values (60% and 71%) were recorded about the ability of the device in differentiating mild dysplasia vs lack of dysplasia and moderate/severe dysplasia vs absence of dysplasia, respectively. The device tested in our study was found to not replace the histopathology procedure. However, we assessed its usefulness for oral tissue examination, especially within an oral medicine secondary care facility, before performing a biopsy and in monitoring oral lesions.
Sexual hormones play an important role in expression of genes involved in a wide variety of biological and neoplastic processes. The information on Estrogen Receptors (ER) expression in non-target tissues is very few and, in particular, the studies in head and neck tumors are still controversial. Recent studies analyzed the role of Tamoxifen (TAM) on Oral Squamous Cell Carcinoma (OSCC) lines in relation to the presence/absence of ER. The purpose of the present study was to evaluate the expression of sexual hormones receptors mRNAs, in particular Estrogen Receptor alpha (ERα) and Androgen Receptor (AR) mRNA in OSCC tissues. The study group comprised 20 samples of OSCC, harvested from 20 otherwise healthy subjects (14 males and 6 females, mean age 58.2y, range 38-74). The control group was formed by 20 samples of normal mucosa harvested around the margins of the specimens (at least 1 cm from the lesion margins). Estrogens Receptor alpha (Era) and Androgen Receptor (AR) mRNA expressions were analyzed by RT-PCR carried out on total RNAs extracted from both cancerous and healthy tissues. Obtained data were evaluated by Shapiro-Walk normality test and compared by Student’s t test. Results with p<0.05 were considered statistically significant. AR transcripts were less expressed in OSCC specimens than in healthy tissues, while levels of ERα transcripts significantly increased in tumor samples. These preliminary data show different expression patterns of AR and ERα mRNAs in malignant tissues of oral mucosa and could suggest an involvement of these sexual hormones in oral cancer.