日時：9月5日（金）12:50 ～ 18:30
会場：ポスター会場（会議場1階　イベントホール）

モリタ優秀発表賞審査「留学生部門」（MP1-79 ～ 95）

MP1-79　「PRIP deficiency promotes YAP nuclear translocation enhancing tissue fibrosis」

袁 美群[1]、佐野 朋美[1]、溝上 顕子[2]、高 靖[3]、兼松 隆[1]
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Fibrosis is characterized by excessive accumulation of extracellular matrix components. Accumulating evidence has highlighted the critical role of YAP/TAZ in the regulation of fibrogenesis. Phospholipase C-related catalytically inactive protein (PRIP) is widely expressed in organs and is involved in numerous cellular processes. PRIP has been shown to inhibit PI3K/AKT signaling, a downstream pathway of TGF-β signaling. Here, we investigated the function and mechanism of PRIP in fibrosis. Wild-type (WT) and Prip-knockout (KO) mice were treated with angiotensin II to induce tissue fibrosis. Prip-KO mice showed significantly increased collagen deposition in the kidney and heart compared to WT mice. Mouse embryonic fibroblasts (MEFs) derived from WT and Prip-KO mice were treated with TGF-β1 and showed that PRIP deficiency upregulated the expression of fibrosis markers. In addition, cell migration was accelerated in Prip-KO MEFs. PRIP deficiency-promoted PI3K/AKT activation facilitated the phosphorylation of MST2 at threonine 117 compared to that in WT MEFs. Subsequently, p-MST2 (Thr117) decreased YAP phosphorylation and increased YAP nuclear translocation, leading to tissue fibrosis.

MP1-80　「Neutrophil elastase release in the trigeminal ganglion induced by trigeminal nerve root compression contributes to orofacial pain hypersensitivity」

Yue Zhou[1]、Hitomi Suzuro[1]、Koichi Iwata[1]、Masamichi Shinoda[1]
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Trigeminal neuralgia is primarily caused by vascular compression of the trigeminal root. However, the pain mechanism remains unclear. This study aims to elucidate the role of neutrophils in the trigeminal ganglion (TG) in the pathogenesis of trigeminal neuralgia. A glass rod was inserted through the rat skull to compress the left trigeminal nerve root (TNC group). No compression was applied in the sham group. On day 7 after TNC, mechanical head-withdrawal threshold (MHWT) decreased compared with sham group. The number of TG neurons immunoreactive (IR) for the neuronal damage marker ATF3 and the amount of neutrophil elastase (ELA2) in the TG were both increased in the TNC group. The ELA2 receptor PAR2 was expressed in TG neuron. The number of ELA2-IR neutrophils was also increased in the trigeminal nerve root. ELA2 or PAR2 inhibition in the TG, as well as systemic administration of carbamazepine, a medication for trigeminal neuralgia, attenuated the TNC-induced decrease in MHWT. These results suggest that TNC-induced neuronal damage and accumulation of ELA2-producing neutrophils in the TG probably activates PAR2-expressed TG neurons, contributing to orofacial pain hypersensitivity.

MP1-81 「Testosterone-mediated downregulation of fatty acid synthesis suppresses microglial inflammation in a sex-specific mechanism」

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Emerging evidence suggests that chronic inflammatory conditions such as obesity and periodontitis may exacerbate Alzheimer's disease (AD) through systemic inflammation, highlighting the importance of inflammatory immune signaling pathways . AD has marked sex differences, with women having a higher prevalence and severity of the disease. This study investigated the role of testosterone in regulating sex-specific microglial inflammation via miRNA-mediated pathways. Hippocampal microglia male and female mice revealed significant sex differences in miRNA expression via microarray analysis, with males showing greater changes, particularly in miRNAs targeting fatty acid synthesis. MG6 microglial cells showed that testosterone upregulates male-enriched miRNAs and suppresses the expression of fatty acid synthase (FASN). This testosterone-induced FASN downregulation attenuated NF-κB/p65 phosphorylation and reduced TNF-α secretion after LPS-induced inflammation. These findings reveal the anti-inflammatory role of testosterone in male microglia via the miRNA-FASN-NF-κB axis, which may attenuate AD susceptibility. The study provides insight into AD pathogenesis and therapeutic strategies.

MP1-82 「メカニカルストレスが歯肉上皮細胞のpro-IL-1β発現におよぼす影響」

Chengwei Li[1]、井上 博[1]、寒川 延子[1]、合田 征司[1]
([1]大歯大 生理)

【目的】ブラキシズムは歯ぎしりや食いしばりによる過度なメカニカルストレス（MS)で歯や顎、歯周組織に影響を及ぼし、歯の動揺や歯肉退縮、さらには心血管系など全身への影響も報告されている。歯槽骨や歯根膜への影響は多く研究されているが、同様の力が歯肉上皮細胞に与える影響は不明である。本研究ではヒト歯肉上皮細胞株Ca9-22を用い、MSがpro-IL-1β発現に与える影響とそのシグナル伝達経路について検討した。

【方法】Ca9-22細胞をType Ⅳコラーゲンでコートしたシリコンチャンバーに播種し、10%FBS存在下で培養した。80～90%の密度に達した後、5Hz・20%伸展率で、10分伸展・10分休止を1サイクルとし、計5サイクル伸展刺激を加えた群を実験群、伸展を行わず静置した細胞を対照群とした。刺激終了後、37℃で20分間静置しサンプルを回収した。Pro-IL-1β発現および関連タンパク質のリン酸化をウェスタンブロッティング法で解析した。

【結果】(1) MSによりpro-IL-1β発現が上昇した。(2) MSによりFAK, p130Cas, ERK 1/2のリン酸化が誘導された。(3) MSにより自然免疫応答を誘導する細胞内受容体NOD2の発現が上昇した。

【考察】ヒト歯肉上皮細胞Ca9-22におけるMSによるpro-IL-1β発現とNOD2発現上昇にはFAK, p130Cas, ERK 1/2のリン酸化が関与している可能性が示唆された。

【利益相反】本研究において開示すべき利益相反関係にある企業はない。

MP1-83 「Effects of metabolites of indigenous oral bacteria *Veillonella* species on the proliferation of normal and oral squamous cell carcinoma cells」

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Introduction: The effects of metabolites of major periodontopathic bacteria, such as Porphyromonas gingivalis, on host cells have been well investigated, but the effects of others are unclear. Therefore, we investigated the effects of Veillonella species—indigenous bacteria commonly less associated with the pathogenicity of oral diseases—on host cells.
Methods: V. atypica (Va) was cultured anaerobically, and the culture supernatant was obtained. HaCaT (normal cell) and HSC2 (cancer cell) were cultured with the filtered supernatant of Va, and the effect on their proliferation was evaluated. Similarly, the effect of propionate, the most abundant metabolite detected in the supernatant, was evaluated.
Results and Conclusion: Va supernatant inhibited the proliferation of both cells, and the inhibition rate was higher in HSC2 than in HaCaT cells. Propionate similarly inhibited both cells, suggesting that it may be one of the responsible substances for the inhibition. In further, the effect on HSC2 was observed in earlier days (≤1 days) and under lower concentrations (≤2.5 mM) compared to HaCaT, suggesting that propionate at a certain concentration may selectively inhibit cancer cells.

MP1-84 「Growth Inhibitory Effect of 5-Aminolevulinic Acid on Cariogenic Bacteria」

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5-Aminolevulinic acid (5-ALA), one of the amino acids, is metabolized within bacterial cells, leading to intracellular accumulation of porphyrins. When these porphyrins are irradiated with specific wavelengths of light, they generate reactive oxygen species (ROS), such as singlet oxygen, which exert cytotoxic effects against bacteria. This mechanism is being actively investigated for its clinical applications in photodynamic therapy (PDT). In our studies focusing on PDT targeting cariogenic bacteria, specifically Streptococcus mutans and Streptococcus sobrinus, we discovered that the simple addition of 5-ALA phosphate to the culture medium inhibits bacterial growth even in the absence of light irradiation. Furthermore, this growth inhibitory effect was observed exclusively under aerobic conditions, suggesting that oxidative stress or metabolic disruptions triggered by oxygen presence may be involved. Currently, we are conducting detailed investigations into this novel antimicrobial mechanism of 5-ALA, which does not depend on photoactivation.

MP1-85 「Osteogenesis imperfecta-specific stem cells exhibit cell cycle dysfunction via p21」

Arwa Mohamed Aboelmaged[1]、Yukari Kyumoto-Nakamura[1]、M Majed Sharifa[1]、Liting Yu[1]、Lisha Dai[1]、Ying Liu[1]、Mhd Fouad Zakaria[1]、Soichiro Sonoda[1]、Hiroki Kato[1]、Takayoshi Yamaza[1]
([1]Kyushu Univ Fac Dent Sci, Sect Mol Cell Biol Oral Anat)

Background: Osteogenesis imperfecta (OI) disrupts extracellular matrix integrity via defective type I collagen, impairing skeletal growth. While growth plate (GP) failure in long bones is established, the role of stem cells/progenitor cells in the GP remains unclear in OI pathology.

This research aims to identify the cell cycle regulation of OI-specific stem cells (OI-SCs).
Methods: We analyzed the cell cycle condition, its related molecules, and their proteolytic status in our established OI-SCs by flow cytometry, western blotting, and immunofluorescence.
Results:OI-SCs exhibited delayed G1/S transition associated with nuclear accumulation of p21. The p21 degradation was impaired due to proteasomal dysfunction in OI-SCs.
Conclusion: Aberrant p21 stabilization via defective proteasomal degradation contributes to the cell cycle dysregulation in OI-SCs. This dysregulation may underlie OI pathology and represents a target for therapeutic intervention.

MP1-86　「BMP9による解糖系活性化と乳酸シグナルを介した骨分化制御機構」

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Bone morphogenic protein 9 (BMP9)は、BMP2やBMP4を凌駕する強力な骨誘導能を有することが報告されてきたが、BMP9による骨分化能の特異性を説明づける分子機構は十分に解明されていない。我々は、骨芽細胞が骨基質を形成する成熟骨芽細胞へと分化する過程において、糖代謝による大量のエネルギー産生が不可欠である点に着目した。そこでマウス骨芽細胞株MC3T3E1, ヒト骨芽細胞株MG63にBMP2、BMP4、BMP9による分化を誘導し、エネルギー代謝の細胞外フラックス解析、細胞内代謝物のメタボローム解析、RNA-seq解析を行ったところ、BMP9はBMP2やBMP4に比べて解糖系の活性化が顕著であり、ATPと乳酸の産生量が著しく増加していることが分かった。BMP9はKLF4、NFATC2等による特徴的な複数の転写因子の発現誘導を介し、解糖系初期に関与するHexokinase 2 (HK2)の発現レベルを上昇させ、解糖系のドライバーとして機能させていた。さらに、BMP9による乳酸産生の増加は、乳酸によって安定化されるシグナル伝達因子であるNDRG3と、ヒストン修飾の一種であるヒストンラクチル化を顕著に上昇させており、それぞれがBMP9誘導性の骨分化関連遺伝子の発現上昇に寄与していた。このようにBMP9は基盤的なATP産生、乳酸を介して活性化されるNDRG3シグナル、ヒストンラクチル化という骨分化促進を担う３つ組を同時に活性化することで、強力な骨分化能を発揮していると考えられる。

MP1-87　「魚鱗ゼラチンの粘稠度が左右する骨形成特性の差異　―骨幅と緻密骨様骨量の視点から―」

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【目的】骨の局所再建において、成長因子などのシグナル分子をその場に保持する足場材料の開発は重要な課題である。我々は、骨形成促進因子を注射により標的部位に投与して骨幅を増加させる新たな治療法の開発を進めているが、足場材料の粘稠度が新生骨の形成様式に与える影響は十分に検証されていない。本研究では、粘稠度の異なる足場材料が骨伝導能に及ぼす効果を明らかにすることを目的とした。
【方法】魚鱗由来ゼラチンを0.1、0.3、0.5 mg/mlの3濃度で調製し、粘稠度を測定した。各ゼラチンにBMP-2 (0.3 μg) とRANKL結合ペプチド (0.66 mg) を含浸させ、8週齢C57BL/6Jマウスの上顎切歯と第一大臼歯間に注入した。4週後にμCT像を取得し、ImageJで新生骨の幅と骨量を定量評価した。また、新生骨と母骨の境界は、蛍光ラベルによるラベリング像で確認し、von Kossa染色で石灰化骨量を測定した。統計解析はShapiro-Wilk検定で正規性を確認後、ANOVAとTukey検定を用いた。
【成績】せん断速度3/sにおける粘稠度は約20、400、2000 mPa・sであった。新生骨幅は低粘稠度群で0.23±0.11 mm、高粘稠度群で0.06±0.02 mmとなり、有意に増加した（＋283%、$p<0.05$)。緻密骨様骨量は低粘稠度群33.29±1.90%、高粘稠度群66.79±2.34%で、有意に減少した（－50%、$p<0.05$)。
【結論】低粘稠度の足場材料は骨幅の拡大に寄与し、高粘稠度の材料は緻密骨様骨の形成を促進する可能性が示唆された。

MP1-88 「CCN3 Knockout Reduces Osteoarthritis Severity in Mice by Preserving Cartilage Matrix Components」

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Osteoarthritis (OA) is a common degenerative joint disease characterized by cartilage degradation, synovial inflammation, and subchondral bone remodeling. Our previous studies showed that CCN3 expression increases with age in knee cartilage, and cartilage-specific overexpression of CCN3 induces senescence-associated secretory phenotype (SASP) and OA-like changes. Here, we examined the effects of CCN3 deletion on OA development in a murine model of destabilization of the medial meniscus (DMM). Histological analysis revealed that CCN3 knockout (KO) mice exhibited reduced cartilage degradation and proteoglycan loss. Gene and protein analyses demonstrated that CCN3 knock out suppressed matrix-degrading enzymes production (MMP-13, ADAMTS-5) and attenuated cartilage degradation. Immunofluorescence showed increased Ki-67 expression in KO OA cartilage, indicating enhanced chondrocyte proliferation. In wild-type OA samples, colocalization of CCN3 and CD44 suggested a possible interaction affecting chondrocyte function. These findings suggest that CCN3 contributes to OA progression, making it a potential therapeutic target.

MP1-89 「Identification and characterization of a novel bone resorption modulator in c-Src/p130Cas axis」

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Podosome formation is essential for osteoclastic bone resorption, serving as the structural basis for the sealing zone that enables bone resorption. Mice lacking conventional c-src or its adaptor p130Cas specifically in osteoclasts exhibit osteopetrosis caused by impaired osteoclastic bone resorption due to defective podosome formation. We previously showed that c-Src and p130Cas form a complex with Pyk2. To identify novel effectors of this complex, we performed anti-Pyk2 immunoprecipitation followed by mass spectrometry using osteoclasts from WT, c-srcKO, and p130CasΔOCL-/- mice. Through a series of immunoprecipitation experiments, we narrowed down the candidates to 18 proteins, we focused on molecule X, which plays a critical role in actin cytoskeleton remodeling. Knockdown of X in RAW264.7 or bone marrow-derived cells resulted in reduced actin ring formation, impaired multinucleation, and diminished bone resorptive activity. Immunofluorescence analysis revealed that X colocalizes with p130Cas at the actin ring, and co-immunoprecipitation demonstrated that X is a downstream effector of c-Src/p130Cas signaling, regulating actin ring formation and osteoclastic bone resorption.

MP1-90 「Elucidation of the physiological role of p130Cas in palatogenesis」

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Palatogenesis is a complicated and intricate process involving multiple morphogenetic events, and its disruption can result in cleft palate, a common congenital anomaly. In this study, we investigated the role of p130Crk-associated substrate (p130Cas), an adaptor protein involved

in integrin and cytokine signaling, during palate development. Analysis of published RNA-Seq dataset confirmed that p130Cas expressed in palatal shelves. Using tamoxifen- inducible p130Cas-deficient mice (p130Cas$^{flox/flox}$ x CAG-Cre/ERTM), we found that p130Cas-deficient embryos exhibit cleft palate between embryonic day (E) 16.5 and E18.5, with palatal shelf growth arrested in the horizontal direction. Histological analysis revealed delayed elevation of the palatal shelves at E14.5, and immunostaining for Ki-67 showed reduced cell proliferation at the same stage. Furthermore, bulk RNA sequencing demonstrated significant downregulation of genes associated with key developmental pathways. These findings indicate that p130Cas is essential for promoting cell proliferation and regulating the proper elevation and fusion of the palatal shelves during palatogenesis.

MP1-91 「Novel expression and role of IRR in dental pulp stem cells」

Ying Liu[1]、Yukari Kyumoto-Namakura[1]、M.Majd Sharifa[1]、Liting Yu[1]、Arwa Mohamed Aboelmaged[1]、Lisha Dai[1]、Mhd Fouad Zakaria[1]、Soichiro Sonoda[1]、Hiroki Kato[1]、Takayoshi Yamaza[1]
([1]Kyushu Univ Fac Dent Sci, Sect Mol Cell Biol Oral Anat)

Object: Dental pulp stem cells (DPSCs) possess the odontoblast differentiation capacity, responsible for dentin formation. Insulin receptor-related receptor (IRR) is known as an alkaline pH sensor, assuming the association with dentin mineralization. Here, we aim to verify the expression of IRR in rat DPSCs and explore its potential role in odontoblast differentiation.
Methods: We isolated DPSCs from dental pulp tissues of rat incisors and cultured them under temporal and periodic alkaline stimulation (pH 7.4 and pH 8.4). We then analyzed IRR expression and assessed odontoblast differentiation.
Results: Rat DPSCs expressed the IRR gene and protein. The temporal and periodic pH 8.4 stimulation could increase the alkaline phosphatase (ALP) activity and induce mineralized matrix deposition by ALP and Alizarin Red S staining. The alkaline stimulation could upregulate the gene expression of bone gamma-carboxyglutamate protein, a late-stage odontoblast marker.
Conclusion: This study is the first to report IRR expression in DPSCs and suggests its responsible role in dentin mineralization.

MP1-92 「Epigenetic regulation of HNF6 in biliary atresia」

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([1]Kyushu Univ Fac Dent Sci, Sect Mol Cell Biol Oral Anat)

Background: Biliary atresia (BA) is a rare congenital bile duct blockage. The unknown molecular pathogenesis makes it hard to develop alternative therapies. Our established BA-specific stem cells expressed elevated hepatocyte nuclear factor 6 (HNF6). This study aims to investigate the epigenetic mechanism of elevated HNF6 in BA-specific stem cells.
Methods: Our established BA-specific stem cells were analyzed by western blot and immunofluorescence (IF) to detect the protein and nuclear localization of candidate transcription factors, Brahma-related gene 1 (BRG1), Brahman (BRM), and nuclear factor kappa B subunit P65 and P50. They were also assessed by chromatin immunoprecipitation-qPCR (ChIP-qPCR) and ChIP-

re-ChIP-qPCR to detect them and their complexes around the HNF6 promoter region.
Results: BRM and nuclear factor kappa B subunit P65 and P50 were enriched around the HNF6 promoter in BA-specific stem cells, but not BRG1. The BRM-P65 complex is significantly bound around the HNF6 promoter in BA-specific stem cells.
Conclusion: The BRM-P65 complex plays a key role in epigenetic chromatin remodeling around the HNF6 promoter in BA-specific stem cells.

MP1-93 「Tumor-derived Apoptotic VesiclesModulate Lymph Node Immune Microenvironment via Fibroblastic Reticular Cells」

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Background: Cancer cells can metastasize early to lymph nodes (LNs), whereas the mechanism of pre-metastatic niche conditioning remains unclear. In this study, we aim to investigate the effects of apoptotic vesicles (ApoVs) derived from dying cancer cells on targeting fibroblastic reticular cells in LNs (LNFRCs), key regulators of LN immunity.
Methods: We isolated LNFRCs from murine LNs. LNFRCs were primed by ApoVs extracted from staurosporine-treated human oral squamous carcinoma cell line HSC-3 cells, which possess a high metastatic potential. ApoV-primed LNFRCs were analyzed for T-cell modulation under coculture with CD3/CD28-activated LN cells.
Results: LNFRCs exhibited stromal and antigen-presenting markers. ApoV-precondition reduced the $CD8^+$ and $CD4^+$ T-cell population one day after coculture and depleted the $CD8^+CD44^+$ high and $CD4^+$ $CD44^+$ population. In contrast, ApoVs induced LNFRC apoptosis after 3 days under serum-depleted conditions.
Conclusion: Cancer cell-derived ApoVs suppress T-cell immunity and viability of LNFRCs. This dual mechanism is suggested to prime LNs for metastasis.

MP1-94 「The role of VEGFR2 expression in oral squamous cell carcinoma progression. 口腔扁平上皮癌における血管内皮細胞増殖因子受容体 2（VEGFR2）発現の働き」

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Vascular endothelial growth factor receptor-2 (VEGFR2) promotes angiogenesis and regulates endothelial cell proliferation through nuclear translocation upon VEGFA binding. In a 4-NQO-induced oral squamous cell carcinoma (OSCC) mouse model, VEGFR2 inhibition (VEGFR2i) delayed progression to SCC, suggesting roles beyond angiogenesis. This study examined VEGFR2 expression and function in OSCC. Spatial transcriptomics revealed elevated VEGFR2 and VEGFA in mouse cancer regions. Immunohistochemistry (IHC) confirmed increased nuclear VEGFR2 and VEGFA with cancer progression, while VEGFR2i reduced proliferation marker expression. In human OSCC, public datasets showed upregulation of VEGFR2 and VEGFA in tumors compared to normal tissues. IHC further revealed positive correlations between nuclear VEGFR2, tumor stage, metastasis, and Ki67 levels. In vitro, VEGFA enhanced cytoplasmic and nuclear VEGFR2 expression and promoted proliferation in both primary mouse SCC and human OSCC cells,

which was suppressed by VEGFR2 blockade. These findings suggest the VEGFA-VEGFR2 axis drives OSCC progression and highlight VEGFR2 as a potential therapeutic target.

MP1-95 「Deamidation of NF-κB p65 at N139 enhances proliferation and anti-apoptotic properties in oral squamous cell carcinoma cells」

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Oral squamous cell carcinoma (OSCC) is the most common malignant tumor of the oral cavity and head and neck region. Deamidation, a post-translational modification, often alters protein structure and function. Two deamidation sites in p65, a subunit of NF-κB, N64, and N139 have been identified in cancer cells, but their roles remain unclear. In this study, endogenous p65 was knocked out (KO) in SCCVII cells using CRISPR-Cas9, followed by transfection with Flag-tagged p65 variants: wild-type (WT), N64D, N139D, and double mutant (N64D/N139D; DD). Luciferase assays showed that N139D and DD mutants significantly reduced p65 transcriptional activity, while N64D had no effect, suggesting that deamination at N139 (N139D) is critical for regulating the transcriptional activity of p65. Stable cell lines expressing Flag-tagged WT, N64D, N139D, and DD were generated. Compared to WT, N139D exhibited the highest proliferation rate, followed by DD, while N64D matched WT. Upon TNFα stimulation, N139D and DD mutants showed enhanced resistance to cell death. These findings suggest that the N139D mutation in p65 positively regulates proliferation and anti-apoptotic properties in OSCC cells.