

Chemokine RANTES/CCL5 from

Jawbone Cavitations

- Hidden Interface to Many

Systemic-Immunological Diseases



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What is RANTES?



regulated on activation, normal T cell expressed and secreted





Why is RANTES/CCL5 of interest for dentist?

The critical interplay of

jawbone cavitations/bone marrow defects

and RANTES/CCL5 overexpression

in jawbone areas







Jawbone cavitations

without typical signs of acute inflammation

filled with fatty-degenerated adipocytes

fatty degenerated osteolysis of jawbone - FDOJ

in cases of facial/trigeminal pain is also called "NICO" (Bouquot: Neuralgia inducing cavitational osteonecrosis)



The object of our interest: Morphology and extent of a

Fatty-degenerative osteolysis/osteonecrosis of jawbone (FDOJ)





The guiding question of the presented research was:

Does FDOJ contain inflammatory immune messengers?

Can immune messengers-Cytokines in FDOJpossibly be related to silent inflammation and to systemic diseases?









"Elephant in the room"



Is the local RANTES/CCL5 overexpression in

jawbone marrow defects of interest for general health?









Manibular Nerve



Characteristics of RANTES

RANTES (Regulated upon Activation, Normal T-cell Expressed, and Secreted), CCL-5 = $\underline{chemotactic cytokine} = c\underline{hemokine}$.

RANTES can have detrimental effects via the recruitment of immune cells that enhance inflammatory processes such as arthritis, atopic dermatitis, nephritis, colitis, and other disorders (Appay, V., S. L. Rowland-Jones. 2001. RANTES: a versatile and controversial chemokine. Trends Immunol. 22: 83-87) RANTES targets the central nervous system and is able to cause multiple sclerosis and Parkinson's disease. In targeting mast cells, RANTES

causes allergies, alopecia (marked by hair loss), and thyroid disorders.

(Rossi, D., A. Zlotnik. 2000. The biology of chemokines and their receptors. Annu. Rev. Immunol.





Why is RANTES/CCL5 interesting for general health?

A simple answer is a literature research in GoogleScholar on "DISEAS AND RANTES CCL5"







Distribution of RANTES (pg/ml) in FDOJ of **BC patients** (n=23)



anzheitliche Zahnheilkunde

RANTES/CCL5 mediates cytokine cross-talk in the tumor microenvironment



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RANTES and its role in breast cancer

RANTES has been associated as well with the induction or promotion of cancer (e.g., prostate and breast). Soria, G., A. Ben-Baruch. 2008. The inflammatory chemokines CCL2 and CCL5 in breast cancer. Cancer Lett. 267: 271-285

....development of breast cancer is the potential ability of RANTES, to act directly on the tumor cells and to promote progression of the tumor. Niwa, Y. et al. Correlation of Tissue and Plasma RANTES Levels with Disease Course in Patients with Breast or Cervical Cancer. ClinCancer Res February 2001 7; 285.

".. analysis of RANTES expression demonstrates that expression of RANTES in breast tumor cells is elevated significantly...

breast tumor cell-derived RANTES may promote breast cancer progression."

Azenshtein E. et al The CC chemokine RANTES in breast carcinoma progression: regulation of expression and potential mechanisms of promalignant activity. Cancer Res. 2002 Feb 15;62(4):1093-102.).





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RANTES/CCL5 expression in FDOJ in 23 BC cases is

- 35-fold higher than in normal jawbone
- 5-fold higher than in BC tissue

"The body's own stem cells stimulate cancer cells to mutate, to spread and to form tumors in other organs...This enhanced metastatic ability is reversible and is dependent on

CCL5/RANTES signaling..."

Karnoub AE., et al. Mesenchymal stem cells within tumourstroma promote breast cancer metastasis. Nature, Volume 449, Issue 7162, pp. 557-563 (2007).



7 cytokines in retromolar area with **metastasis of BC** compared to normal jawbone (n=19)

Pathohistology: "Metastasis of adenocarcinoma of breast cancer in jawbone"

195.5

27.6

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FGF-2 IL-1ra IL-6 IL-8 MCP-1 TNFa RANRESITES reg 38-39





Left panel: retromolar area after decortication shows fatty bone marrow

Right panel: lump of fatty-degenerated Osteolysis/osteonecrosis of bone marrow



RANTES/CCL5 and its role in BC metastasis

...RANTES can also increase the metastatic potential of cancer cells.

Eissa S.A.L. et al. Importance of Serum IL-18 and RANTES as Markers for Breast Carcinoma Progression, Journal of the Egyptian Nat. CancerInst., Vol. 17, No. 1, March: 51-55, 2005.

...BC cells stimulate secretion of RANTES from mesenchymal stem cells, which then acts on cancer cells to enhance their motility, invasion and metastasis.

Karnoub, A et al. Mesenchymal stem cells within tumourstroma promote breast cancer metastasis, Nature, Volume 449, Issue 7162, pp. 557-563 (2007).

...this increased propensity towards metastasis is reversible and dependent on the RANTES signaling.

Azenshtein E. et al The CC chemokine RANTES in breast carcinoma progression: regulation of expression and potential mechanisms of promalignant activity. Cancer Res. 2002 Feb 15;62(4):1093-102.).



Immunohistochemic staining of FDOJ

- jawbone marrow defects

The visible prove

of RANTES/CCL5 signaling pathway

connection from jawbone to tumors



We generated a panel of **anti-RANTES monoclonal antibodies** for immunohistologic staining of RANTES expression in jawbone.

Most normal adult tissues contain few, if any, RANTES positive cells.

In contrast, RANTES expression dramatically increases in inflammatory sites. In addition, megakaryocytes and some tumours, express high levels of RANTES message and protein.

von Luettichau I at al. RANTES chemokine expression in diseased and normal human tissues. Cytokine. 1996 Jan;8(1):89-98.

These results indicate a wider expression of RANTES than previously appreciated and suggest multiple physiologic roles for this soluble factor.



Female, aged 51 years; clinical diagnosis: Breast cancer







Female, aged 63 years; clinical diagnosis: Breast cancer





Duct-invasive breast carcinoma with RANTES/CCL5-positive tumor cell nests (arrows).

The staining is not as strong as in the FDOJ samples.





Breast cancer and associated connective adipose tissue.

There are also distinct RANTES/CCL5-stained cells,

while the breast cancer epithelial tracts show only mild-to-moderate, non-specific background staining.



CCR5/CCL5 axis interaction promotes migratory and invasiveness of pancreatic cancer cells Santosh Kumar Singh, Manoj K. Mishra, Isam-Eldin A. Eltoum, Sejong Bae, James W. Lillard Jr. & Rajesh Singh Scientific Reports 8, Article number: 1323 (2018)



If chronic inflammation, per se, were a sentinel event in the transformation of a normal cell to a cancer cell, one would expect a high incidence of cancer in patients with chronic arthritis, but that is not evident. **Why?**

The answer is:
RANTES/CCL5
and NOT TNF-a
is possibly the signal
for cancer development
Lechner J, Schuett S, von Baehr V. "Aseptic-avascular osteonecrosis: local "silent inflammation" in the jawbone and RANTES/CCL5 overexpression. Clinical, Cosmetic and Investigational Dentistry 2017:9 99–109.

	TNF-a	IL-6	RANTES
Rheumatoid arthritis	+++	++	+
Osteoporosis	+++	++	-
Obesity	+++		-
Periodontitis	+++	++	+
Peri-implantitis	+++	++	-
Biphosphonate-induced			
osteonecrosis	++	++	-
Fottu de generative este presie			
rally-degenerative osteonecrosis	-	-	+++



RANTES–levels in CerebroSpinalFluid (CSF) of MS-patients



"CSF levels of RANTES were remarkably high only in active MS patients....

RANTES correlates with inflammation and synaptic excitability in MS brains."

Mori F, et al. <u>RANTES correlates with inflammatory activity and synaptic</u> <u>excitability in multiple sclerosis</u>. <u>Multiple</u> Sclerosis Journal1–8; DOI: 10.1177/ 1352458515621796



Female, aged 58 years; clinical diagnosis: ALS



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....in order to investigate whether RANTES as index of immune activation is present in ALS patients.

Patients with ALS had higher RANTES levels compared with the NoneIND patients and CTRL subjects in serum.

CSF RANTES levels were also higher compared with the NoneIND patients.

These results may suggest an activated microglia induced recruitment of peripheral inflammatory cells to sites of inflammation in ALS patients.

(<u>Rentzos M</u>, et al. RANTES levels are elevated in serum and cerebrospinal fluid in patients with amyotrophic lateral sclerosis. <u>Amyotroph Lateral Scler.</u> 2007 Oct;8(5):283-7.)



Comparision of 7 cytokines in ALS patientsn (n=5) in FDOJ and in normal jawbone marrow (n=19) in pg/ml





FDOJ – chronic inflammation in jawbone

a) FDOJ is characterized by fatty degenerative softening and osteolysis and osteonecrosis of jawbone

b) FDOJ is characterized by degeneration of adipocytes, metabolic disturbance and total lack of typical leukocytic inflammation

c) FDOJ is characterized biochemically by high levels of proinflammatory RANTES/CCL5 in comparision to normal jawbone.

d) FDOJ is characterized by absence of acute cytokines such as TNFalpha and IL-6, which explains the painless and cryptic nature of FDOJ.

Data presented support our hypothesis:

- There are hyperactive signaling pathways through RANTES expression in jawbone cavitations
- FDOJ sites promote pathogenesis and metastasis of BC as a **silent inflammation**
- Surgical debridement of FDOJ in jawbone
 is eliminating RANTES sources





Why is FDOJ neclected in dentistry?



Validation of dental X-ray by cytokine RANTES – comparison of X-ray

findings with cytokine overexpression in jawbone

Link in PubMed: http://www.ncbi.nlm.nih.gov/pubmed/25170282





FDOJ sample: Bone marrow of jawbone changed to fatty-degenerative osteonecrosis





Existence of FDOJ is neglected in dentistry because of diagnostic problems in x-rays



Inconspicuous retromolar area

Extent of softened bone marrow in retromolar area Sample of FDOJ in retromolar area





X-ray density area 38/39 preop = 140 X-ray density area 38/39 postop = 138







How to detect and locate cavitations in jawbones?

Or: How to find

the source of chronic

overexpression of

RANTES in jawbone ?





Through-Transmission Alveolar Ultrasonography (TAU).

New TAU® generates an ultrasound pulse and passes the pulse through the jawbone.

The pulse is detected and monitored by an ultrasound receiving unit.

Attenuations of the amplitude of the pulse are indicative for pathological changes in the jawbone.

The results are displayed on a color monitor, showing different colors according to different degrees of attenuation.



CaviTAU®

1= Handpiece with Ultrasoundsender and -sensor unit

2= Ultrasound sender 3= Ultrasound receiver/sensor









CaviTAU® red/geen-imaging of bone density











Lechner J, Noumbissi S, von Baehr V. Titanium implants and silent inflammation in jawbone – a critical interplay of dissolved titanium particles and cytokines TNF-a and RANTES/CCL5 on overall health? EPMA Journal (2018). https://doi.org/10.1007/s13167-018-0138-6

Take home messages

Collectively our data reveal a hitherto unknown function of **chronic inflammation in jawbone** promoting overexpression of **chemokine RANTES/CCL5**

The challenge posed by these discoveries is the need to raise awareness of **jawbone cavitations (FDOJ)** throughout the medical and dental community under the **integrative aspect of "silent inflammation"**.

Interest in

trans-alveolar ultrasound device?

Please refer to <u>www.cavitau.de/</u> in English/ Newsletter and submit with your name and email

Many thanks for your highly appreciated attention

Documentation of fatty-degenerative Osteonecrosis of the Jawbone (FDOJ) in patients with Atypical Facial Pain/Trigeminal Neuralgia

Own scientific literature:

Lechner J, von Baehr V. *Peripheral Neuropathic Facial/Trigeminal Pain and RANTES/CCL5 in Jawbone Cavitation.* Evid Based Complement Alternat Med. 2015;2015:582520. doi: 10.1155/2015/582520. Epub 2015 Jun 11. PMID: 26170877; PMCID: PMC4481083.

Free download under: <u>http://www.hindawi.com/journals/ecam/2015/582520/</u>

Link in PubMed: http://www.ncbi.nlm.nih.gov/pubmed/26170877

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 jawbone density

indispensable instrument for the detection of
 chronic inflammation
 in diseases of the immune system

... used internationally with a worldwide patent certificate

Patient with an atypical pain in the left lower jaw for 7 years

Examination regio 36-39: Vital bone tissue; medullary canals with fibrotic adipose tissue; increased tissue mast lines; trophic disturbances.

Fall #2:

Assessment regio 48/49: Irregular, very delicate spongy bone tissue without evidence of actively increased bone remodelling. In medullary adipose tissue caliber variations of adipocytes and fibrillar as well as mucoid transformation of cytoplasmic contents; matching trophic disorders.

Fall #3:

Atypicial facial pain in the right upper jaw for 3 years with neuroborreliosis

Regio 18-19 in 3D-DVT

Examination of region 18/19: Vital spongy bone tissue; medullary canals fibrosed; fat cells with marked degenerative damage to the cytoplasmic content, marked calibre fluctuations of the adipocytes; fibrillar degeneration; trophic disturbances.

Attacks of neuralgia over the entire facial area for 5 years

Assessment regio 48/49: In medullary canals fatty tissue with **degenerative damage; fibrillar degeneration** of cytoplasmic contents, consistent with trophic disturbances. **No inflammation**.

Fall #5:

Patient with trigeminal neuralgia on the right side of the lower jaw for 7 years

Assessment area 48/49: osteoporosis-like osteopenia; basophilic osseous without inhabited osteocyte cavities; intratrabecular fat marrow only present in remnants; sparsely recorded lymphoid cell nodules; **no expression of inflammation**; nonspecific trauma sequelae.

149,9

3510

Case #5

Fall #6:

Patient has been suffering from atypical facial pain in the right upper jaw for 6 years

Assessment area 48/49: osteoporosis-like osteopenia; basophilic osseous without inhabited osteocyte cavities; intratrabecular fat marrow only present in remnants; sparsely recorded lymphoid cell nodules; **no expression of inflammation**; nonspecific trauma sequelae.

Fall #7:

Patient has been suffering from trigeminal neuralgia in the left upper jaw for 10 years

Assessment of area 18/19: medullary canal with unremarkable haematopoietic bone marrow; **fibrosed adipose tissue with myxoid transformation** of cytoplasmic contents; trophic disturbances.

Fall #8:

Assessment area 36/37: Medullary canal with **myxoid or fibrillar de- generation** of cytoplasm; **peripheral nerve** with perineural sheath fibrosis (**pain symptomatology**?); focally increased proliferated capillaries.

Fall #9:

Patient has been suffering from right mandibular trigeminal neuralgia for 4-5 years

Assessment area 48/49:

Significantly reactive osteosclerotic widened vital bone tissue with little active bone remodelling. Bone tissue with little active bone remodelling. Fat cells with calibre fluctuatons; Fine fibrillar or mucoid transformation of the cytoplasmic space. Slightly increased of lymphocytes and mast cells in the manner of minor chronic osteitis.

Fall #10:

Assessment area 18/19: Vital preserved bone bellows; intratrabecular fat marrow with oedematous fine fibrillar interstitial matrix with degenerative changes; blood vessels with fibrosed adventitia and reactive capillary proliferates and erythrocyte extravasations; no inflammatory infiltrates or exudates; trophic disturbance.

Literature on RANTES/CCL5 and Atypical Facial Pain (selection)

- J. E. Bouquot, A. M. Roberts, P. Person, and J. Christian, "Neuralgia-inducing cavitational osteonecrosis (NICO): osteomyelitis in 224 jawbone samples from patients with facial neuralgia," *Oral Surgery Oral Medicine and Oral Pathology*, vol. 73, no. 3, pp. 307–320, 1992.
- E. J. Ratner, B. Langer, and M. L. Evins, "Alveolar cavitational osteopathosis—manifestations of an infectious process and its implication in the causation of chronic pain," *Journal of Periodontology*, vol. 57, no. 10, pp. 593–603, 1986.
- L. M. Bolin, R. Murray, N. W. Lukacs et al., "Primary sensory neurons migrate in response to the chemokine RANTES," *Journal of Neuroimmunology*, vol. 81, no. 1-2, pp. 49–57, 1998.
- N. Kiguchi, Y. Kobayashi, and S. Kishioka, "Chemokines and cytokines in neuroinflammation leading to neuropathic pain," *Current Opinion in Pharmacology*, vol. 12, no. 1, pp. 55–61, 2012.

Mind breaking new book by Dr. Dr. (PhD) Johann Lechner

Cavitational Osteonecrosis in Jawbone -

From neglected local inflammation to endangering systemic diseases.

ORDER HERE: <u>https://bit.ly/3ryKi2Q</u>

READING SAMPLE: https://bit.ly/3owkWRa

SCOTT M. CHANDLER, DMD | MATTHEW D. GEDDES, DDS

What is a Cavitation?

A cavitation is a hole in the bone, usually where a tooth has been removed, and the bone has not healed/filled in properly. It is an area of osteonecrosis (dead bone), that has a sponge-like quality of very low bone-density.

What's Hiding Inside?

Inside a cavitation, anaerobic bacteria flourish and deviant cells multiply. Cavitations act as a breeding ground for bacteria and their toxins. Research has shown these bacterial waste products are extremely potent and result in digestion problems, chronic fatigue, general feeling of malaise, and other chronic health problems. They often have high levels of *Rantes (CCL-5)*, a protein that has been linked to cancer, MS, Parkinson's etc, etc in recent studies. Cavitations can also cause blockages on the body's energy meridians and can exert far-reaching impact on the overall system. Investigation has revealed that some cavitations are reservoirs of huge amounts of mercury. Cavitations may be a source of low-level or high-level stress on the entire body.

How do we fix them?

Traditionally, these are corrected by surgical intervention where they are debrided, cleaned with laser, ozone, ultrasonic, etc. Then **a-PRF** is placed, which is a supercharged healing clot made from the patients own blood, then held in place with dissolvable sutures.

There is an alternative treatment using Nd:Yag laser to non-surgically treat the affected area 2-3 times over a period of a few months. This method has shown great promise and many patients have felt a noticeable difference in how they feel afterwards. However, there is no long-term data nor research done on this method and currently I am one of 2 or 3 dentists in the country using this technique.

Tooth-Organ Meridian Chart

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															1.5									
Sense Organs	In	ner Ear	Maxillary Sinus		Ethmoid Cells		Еуе	Frontal Sinus		Frontal Sinus		Eye	Ethmoid Cells		d Maxilla Sinus		Inner Ear							
Sha		houlder Flbow	Jaws		Shoulder Elbow			Back of Knee		Back of Knee			Shoulder		Jaws		Shoulder							
Joints	Hand, Ulnar Foot, Plantar Toes, Sacro- iliac Joint		Front of Knee		Hand, Radial Foot Big Toe		Foot		Sacrococcyx Foot		Hip	Hand, Radial Foot Big Toe		Front of Knee		Hand, Ulnar Foot, Plantar Toes, Sacro- iliac Joint								
Spinal Segments	T1 ⁻ S1	C8 T5 T6 T7 1 S2 S3	T11 T12 L1		C5 C6 C7 T2 T3 T4 L4 L5		T8 T9 T10	L2 L3 S4 S5 Coccyx		L2 L3 S4 S5 Coccyx		T8 T9 T10	C5 C6 C7 T2 T3 T4 L4 L5		T11 T12 L1		C8 T1 T5 T6 T7 S1 S2 S3							
Vertebrae	T	C7 1 T5 T6 S1 S2	T11 T12 L1		C5 C6 C7 T2 T3 T4 L4 L5		T9 T10	L2 L3 S3 S4 S5 Coccyx		L2 L3 S3 S4 S5 Coccyx		T9 T10	C5 C6 C7 T2 T3 T4 L4 L5		T11 T12 L1		C7 T1 T5 T6 S1 S2							
Heart-R		leart-R	Pancreas		Lung-R Liver		Liver-R	Kidney-R		Kidney-L		Liver-L	L Lung-L		Spleen		Heart-L							
Organs	Duodenum		enum Stomach-R		Large Intestine-R		Blad Urog A	lder-R Jenital rea	Bladder-L Urogenital Area		Bile Ducts -L	Large Intestine-L		Stomach-L		Jejunum Ileum-L								
Endocrine Organs	Pituitary, Ant. Lobe		Para- thy- roid	Thy- roid	Thy- mus	Pit Pos	uitary, st Lobe	Pinea	l Gland	Pineal Gland		Pitui Post	itary, Thy- Lobe mus		Thy- roid	Para- thy- roid	Pituitary, Ant. Lobe							
Others	F	CNS Psyche	Marr Glai	nmary nd-R									Mam Glar	Латтагу CN Gland-L Psyc		3 1e								
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16							
Upper Teeth	R	M	ß	ß	8		β	8	6	6	8	8	6	6	M	M	Ø	L						
Lower Teeth	R	R	R	R	9	G		9	9	Ø	Q	9	9	9	R	R	R	L						
0:1	F	32	31	30	29 Mamn	28	27	26	25	24	23	22	21 Man	20	19	18	17 Energ							
Utners	Metabolism				Gland-R									ind-L			Metabolism							
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Organs	Ileum-R Ileocea		Ileum-R Large Intestine-R Ileoceal Region		Stomach-R Pylorus Gall- blad- der		Bladder-R Urogenital Area		Bladder-L Urogenital Area		Bile Ducts -L	Stomach-L		Large Intestine-L		Jejuni Ileum	ım -L							
		Heart-R Lung-		ig-R	Pancreas		Liver-R	Kidney-R		Kidney-L		Liver-L	L Spleen		Lung-L		Heart-L							
Vertebrae	T1	C7 T1 T5 T6 S1 S2 C5 C6 C7 T2 T3 T4 L4 L5		T11 T12 L1		T9 T10		2 L3 S4 S5 ccyx	L2 L3 S3 S4 S5 Coccyx		T9 T10	T11 T12 L1		C5 C6 C7 T2 T3 T4 L4 L5		C7 T1 T5 T6 S1 S2								
Spinal Segments	C8 C5 C6 C7 T1 T5 T6 T7 T2 T3 T4 S1 S2 S3 L4 L5		T11 T12 L1		T8 T9 T10	L2 L3 S4 S5 Coccyx		L2 L3 S4 S5 Coccyx		T8 T9 T10	T11 T12 L1		C5 C6 C7 T2 T3 T4 L4 L5		C8 T1 T5 T6 T7 S1 S2 S3									
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Joints	Hand, Ulnar Foot, Plantar Toes, Sacro- iliac Joint Hand, Radial Foot Big Toe		Radial oot Toe	Jaws		Foot		Foot		Нір	Jaws		Hand, Radial Foot Big Toe		Hand, Ulnar Foot, Plantar Toes, Sacro- iliac Joint									
Sense Organs		Ear	Ethi Ce	moid ells	Maxilla Sinu:	ary s	Eye	Frotal Sinus		Frotal Sinus		Frotal Sinus		Frotal Sinus		Eye	Maxillary Sinus		Maxillary Sinus		y Ethmoid Cells		Ear	

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