National Academies of Sciences, Engineering, and Medicine
Virtual workshop on ‘Understanding the Role of the Immune System in Improving Tissue Regeneration’
November 2-3, 2021

Endogenous pro-resolution and pro-regenerative mechanisms in the periodontal tissue

George Hajishengallis DDS, PhD

Thomas W. Evans Centennial Professor

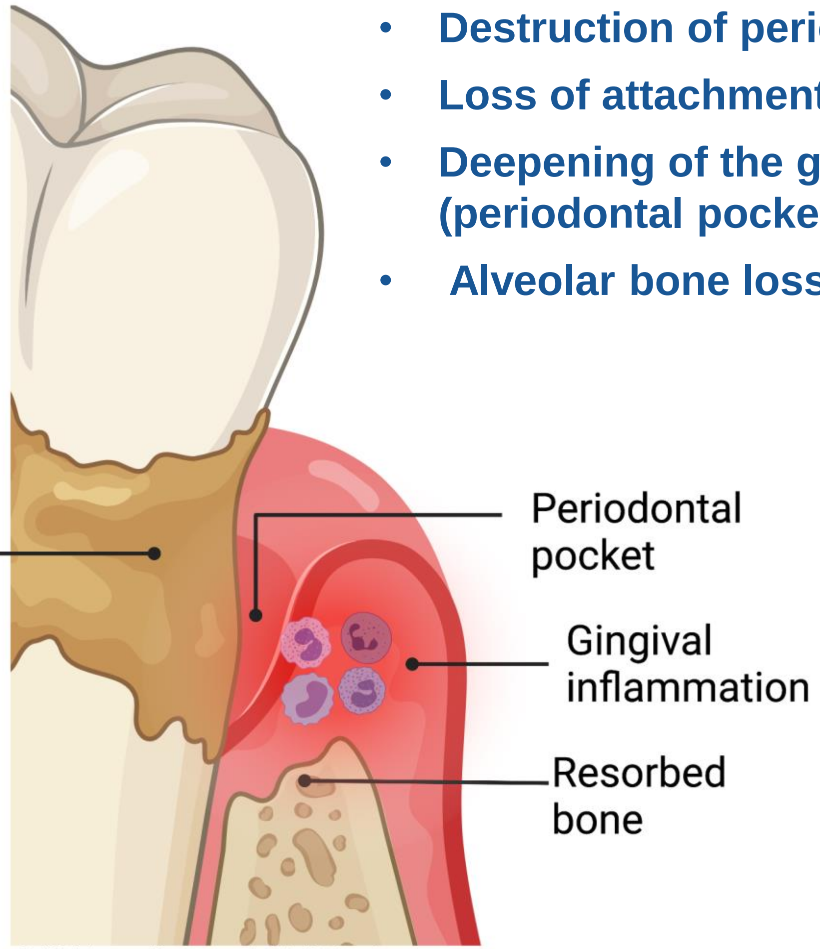
Department of Basic and Translational Sciences

Penn Dental Medicine





Periodontitis: chronic inflammatory disease of the tooth-supporting tissues (periodontium)



G. Hajishengallis, created with BioRender.com

- **Destruction of periodontal ligament**
- **Loss of attachment to the teeth**
- **Deepening of the gingival crevice (periodontal pocket)**
- **Alveolar bone loss**

<u>Severe periodontitis</u>

- **Afflicts 10% of the adult population**
- **6th most prevalent condition worldwide**

Kassebaum et al. 2014, J Dent Res

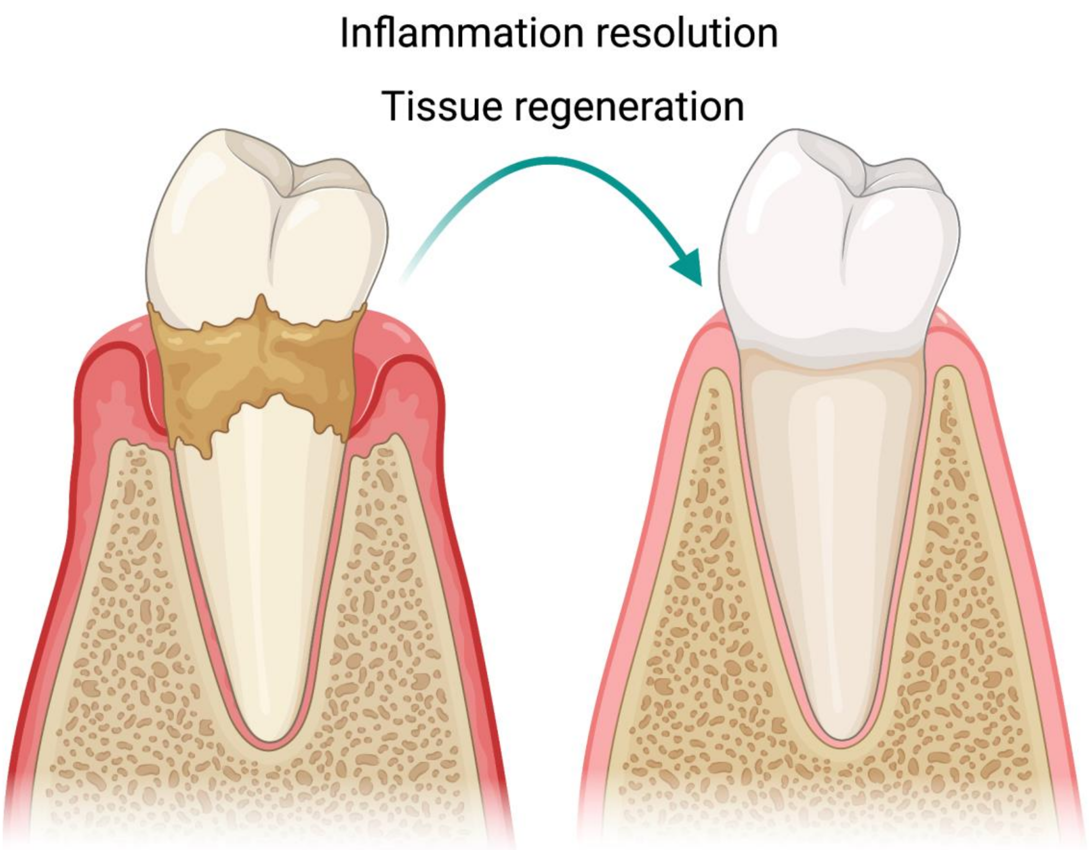
- **Associated with increased risk of systemic comorbidities**

Hajishengallis and Chavakis. 2021, Nat Rev Immunol

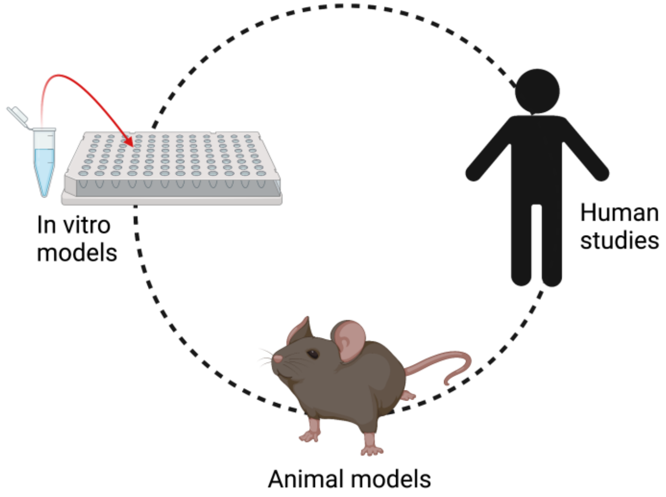
Total cost in USA
(direct & indirect due to productivity losses)
$154.06 billion

Botelho et al. 2021, J Periodontol

Goal: To promote inflammation resolution and tissue regeneration



G. Hajishengallis, created with BioRender.com



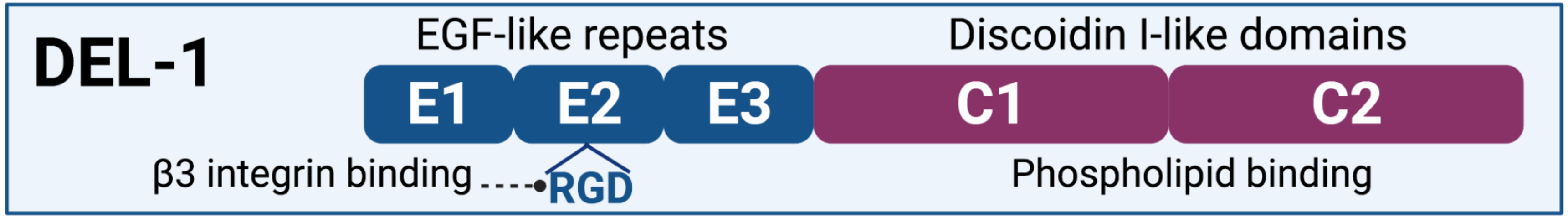
G. Hajishengallis, created with BioRender.com

Phase 2a clinical trial of complement C3 inhibitor AMY-101 in adults with periodontal inflammation

Hatice Hasturk,[1] George Hajishengallis,[2] John D. Lambris,[3] Dimitrios C. Mastellos,[4] and Despina Yancopoulou[5]

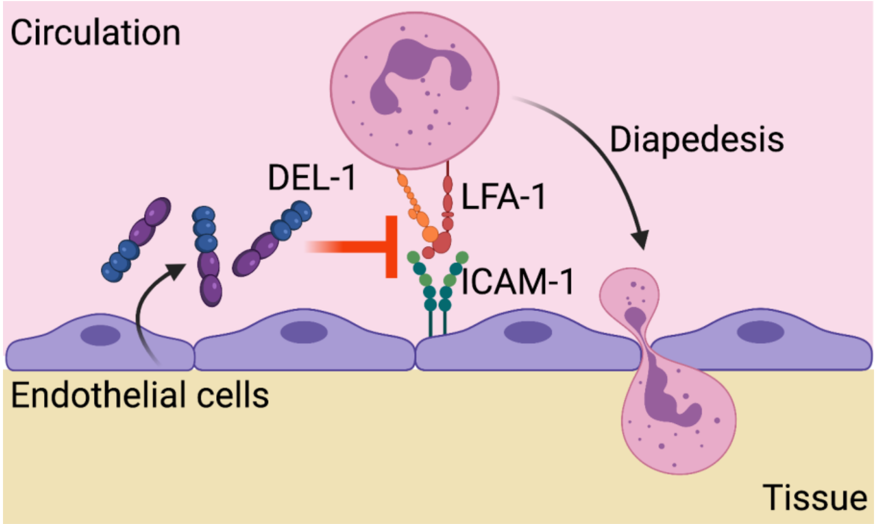
Published October 7, 2021

Developmental endothelial locus-1 (DEL-1)



G. Hajishengallis, created with BioRender.com

- Secreted 52-kDa protein that interacts with αv and β2 integrins and phospholipids.
- Expressed by tissue resident cells, incl. endothelial cells, neuronal cells, MSCs (PDL and bone marrow), and certain macrophage subsets.
- Expression decreases with aging (humans & mice).



G. Hajishengallis, created with BioRender.com

nature immunology

VOLUME 13 NUMBER 5 MAY 2012

The leukocyte integrin antagonist Del-1 inhibits IL-17-mediated inflammatory bone loss

Mehmet A Eskan[1,2], Ravi Jotwani[2], Toshiharu Abe[2,8], Jindrich Chmelar[3], Jong-Hyung Lim[3], Shuang Liang[2], Paul A Ciero[2], Jennifer L Krauss[2], Fenge Li[2], Martina Rauner[4], Lorenz C Hofbauer[4], Eun Young Choi[3,5,6], Kyoung-Jin Chung[3], Ahmed Hashim[7], Michael A Curtis[7], Triantafyllos Chavakis[3,6,9] & George Hajishengallis[1,2,8,9]

RESEARCH ARTICLE

PERIODONTITIS

DEL-1 restrains osteoclastogenesis and inhibits inflammatory bone loss in nonhuman primates

Jieun Shin,[1]* Tomoki Maekawa,[1]* Toshiharu Abe,[1] Evlambia Hajishengallis,[2] Kavita Hosur,[1] Kalyani Pyaram,[1†] Ioannis Mitroulis,[3] Triantafyllos Chavakis,[3‡] George Hajishengallis[1‡§]

www.ScienceTranslationalMedicine.org 30 September 2015 Vol 7 Issue 307 307ra155

Molecular Psychiatry (2015) 20, 880–888

www.nature.com/mp

Multiple sclerosis

ORIGINAL ARTICLE

Developmental endothelial locus-1 is a homeostatic factor in the central nervous system limiting neuroinflammation and demyelination

EY Choi[1,2,3,4,16], J-H Lim[3,16], A Neuwirth[3], M Economopoulou[5], A Chatzigeorgiou[3,4], K-J Chung[3], S Bittner[6], S-H Lee[1], H Langer[2,7], M Samus[4], H Kim[1], G-S Cho[1], T Ziemssen[8], K Bdeir[9], E Chavakis[10], J-Y Koh[11], L Boon[12], K Hosur[13], SR Bornstein[4], SG Meuth[6], G Hajishengallis[13] and T Chavakis[2,3,4,14,15]

Rheumatoid arthritis

JCI The Journal of Clinical Investigation

Stromal cell–derived DEL-1 inhibits Tfh cell activation and inflammatory arthritis

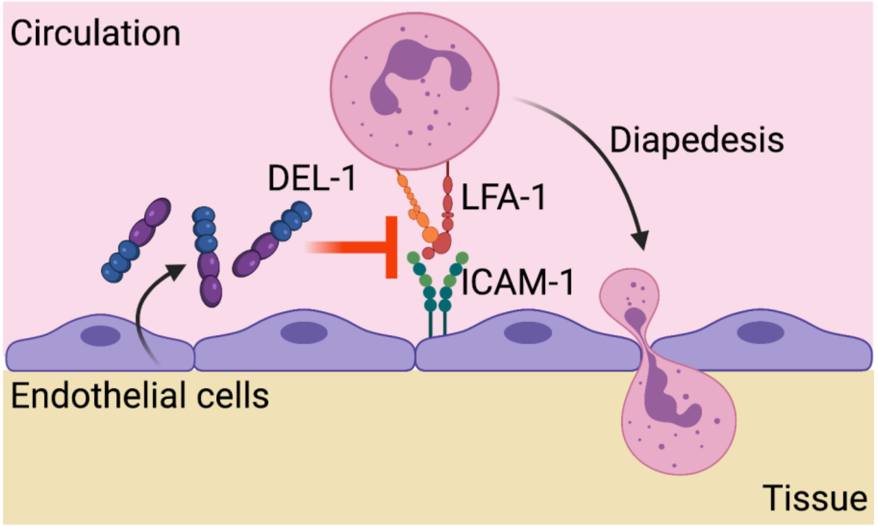
Hui Wang,[1] Xiaofei Li,[1] Tetsuhiro Kajikawa,[1] Jieun Shin,[1] Jong-Hyung Lim,[1] Ioannis Kourtzelis,[2,3] Kosuke Nagai,[2] Jonathan M. Korostoff,[4] Sylvia Grossklaus,[2] Ronald Naumann,[5] Triantafyllos Chavakis,[2,6] and George Hajishengallis[1]

J Clin Invest. 2021;131(19):e150578. https://doi.org/10.1172/JCI150578.

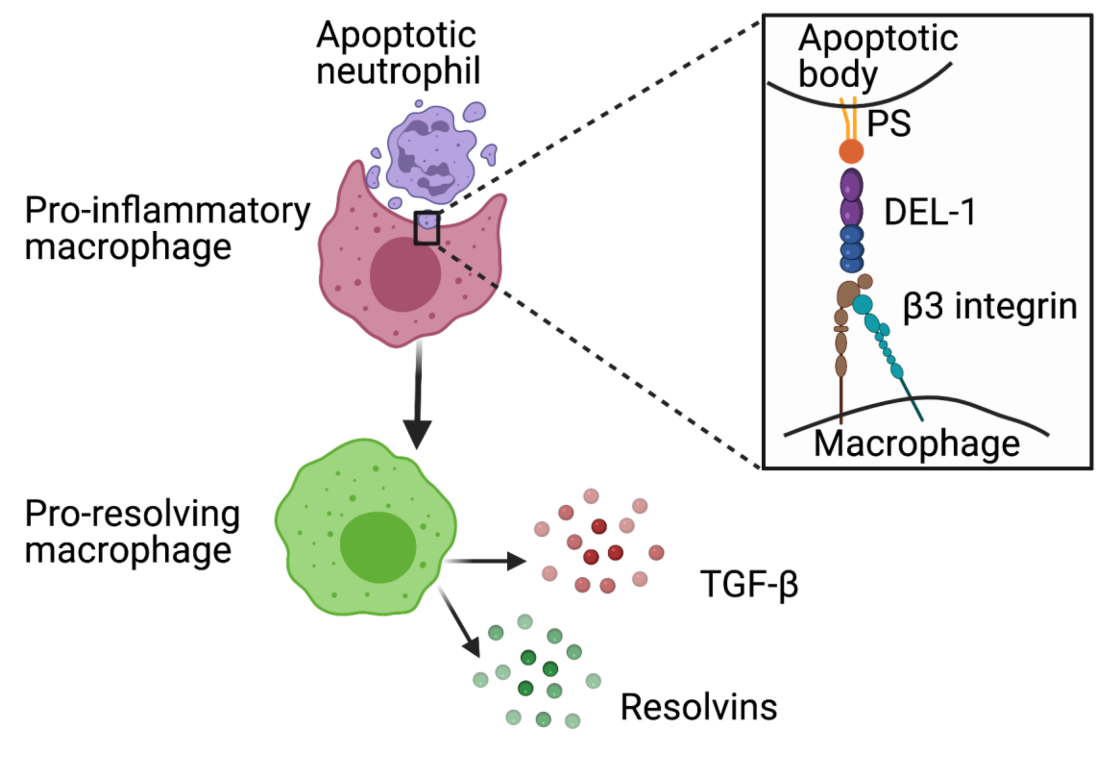
Location matters:

Endothelial-derived DEL-1 regulates the recruitment of neutrophils

Macrophage-derived DEL-1 regulates the clearance of apoptotic neutrophils



G. Hajishengallis, created with BioRender.com

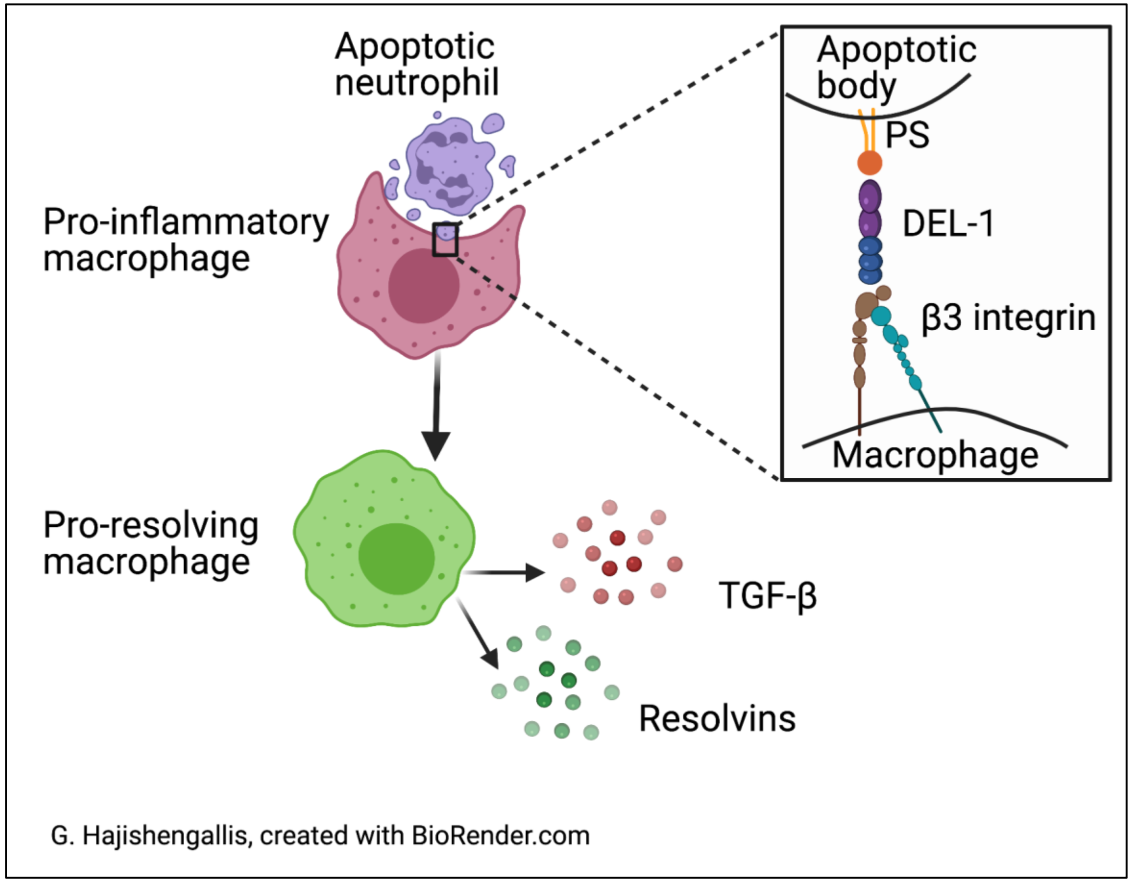


G. Hajishengallis, created with BioRender.com

ARTICLES
https://doi.org/10.1038/s41590-018-0249-1
nature immunology

DEL-1 promotes macrophage efferocytosis and clearance of inflammation

Kourtzelis et al, 2019, Nat Immunol

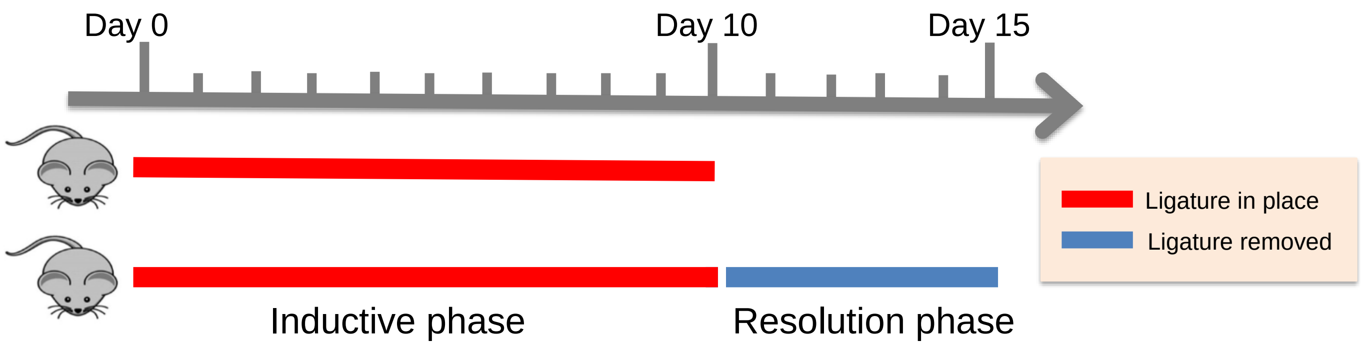


JBC ARTICLE
J. Biol. Chem. (2020) 295(21) 7261–7273

The secreted protein DEL-1 activates a β3 integrin–FAK–ERK1/2–RUNX2 pathway and promotes osteogenic differentiation and bone regeneration

Received for publication, February 13, 2020, and in revised form, April 8, 2020 Published, Papers in Press, April 12, 2020, DOI 10.1074/jbc.RA120.013024

Da-Yo Yuh[‡1], Tomoki Maekawa[‡§], Xiaofei Li[‡], Tetsuhiro Kajikawa[‡], Khalil Bdeir[¶], Triantafyllos Chavakis[‖], and George Hajishengallis[‡2]



Bone regeneration capacity

- WT mice ✓
- *Del1*$^{-/-}$ mice ✗
- *Del1*$^{-/-}$ mice + rDEL-1 ✓
- *Del1*$^{-/-}$ mice + rEGF-like repeats ✓

The effect of DEL-1 to promote bone regeneration is independent of its ability to promote resolution through efferocytosis

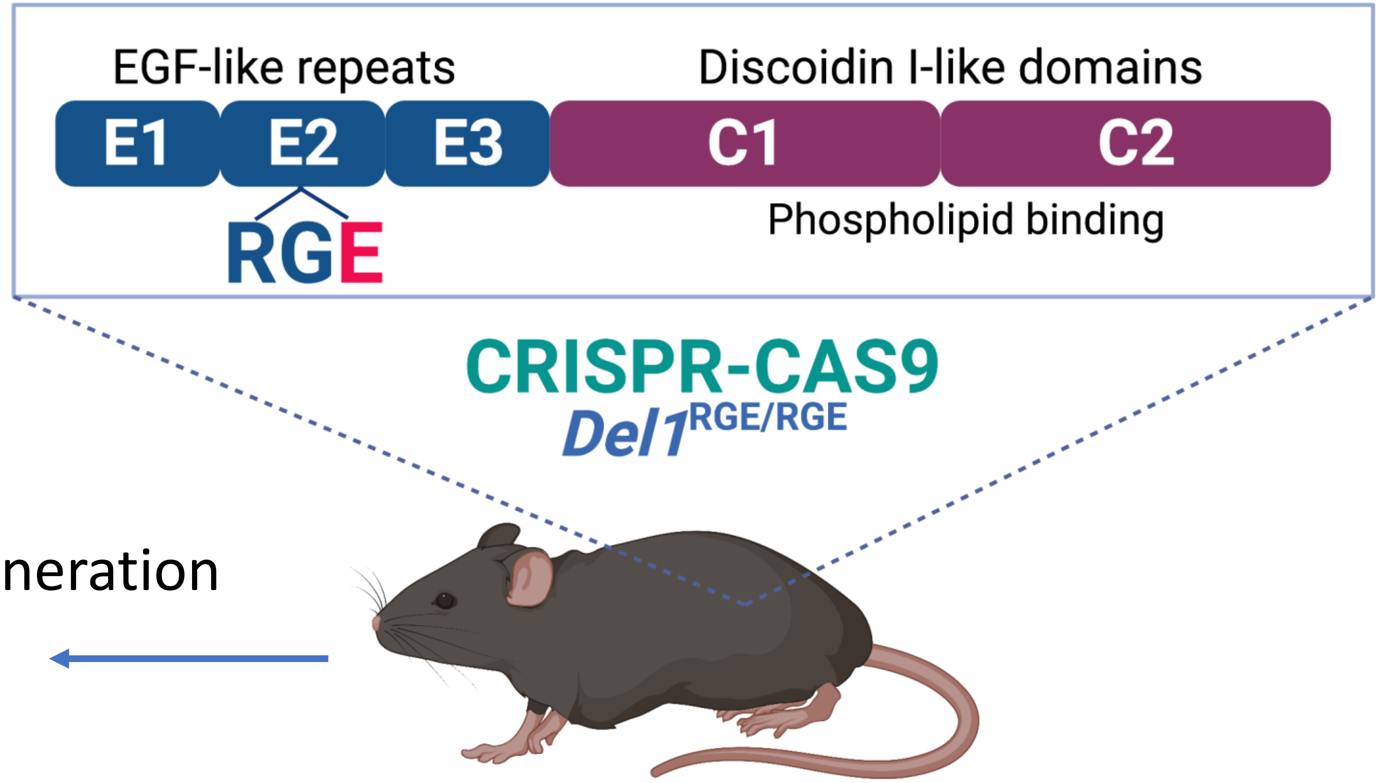
Intact DEL-1 is required for promotion of efferocytosis and inflammation resolution

Kourtzelis et al, 2019, Nat Immunol

The EGF-repeat region of DEL-1 is sufficient to promote bone regeneration

Yuh et al, 2020, JBC

The DEL-1 RGD motif is required for bone regeneration during the resolution phase



Defective bone regeneration during resolution of periodontitis

Yuh et al, 2020, JBC

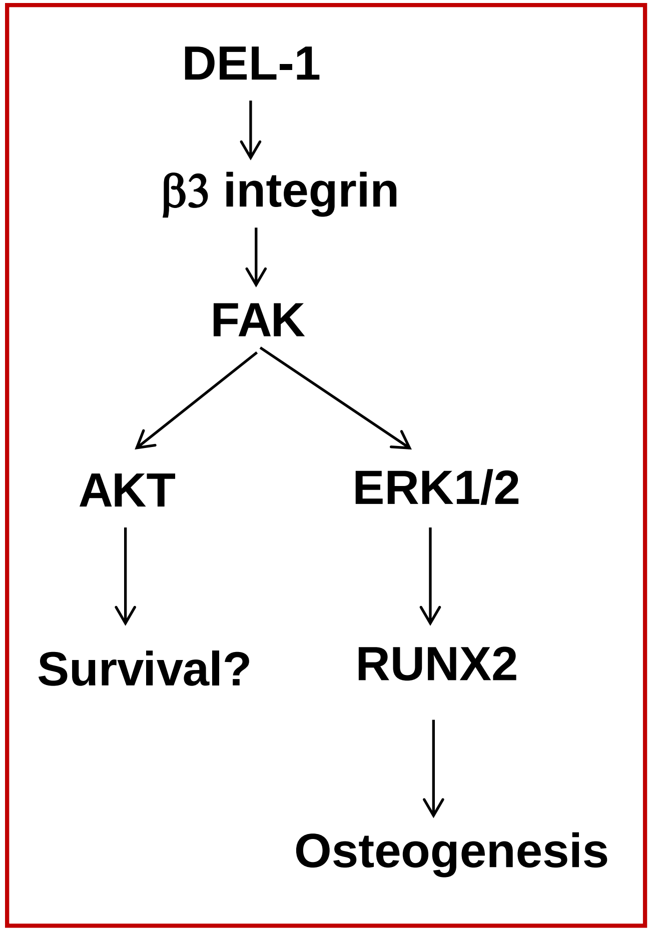
In vitro mechanistic studies

Primary calvarial osteoblastic cells:

The RGD motif and EGF repeats mediate the ability of DEL-1 to induce osteogenic differentiation and calcified nodule formation.

MC3T3-E1 osteoblastic progenitor cells:

DEL-1 promotes osteogenic differentiation and mineralization through a β3 integrin-FAK-ERK1/2-RUNX2 pathway.



Yuh et al, 2020, JBC

Unlike young mice, old mice fail to regenerate bone during periodontitis resolution.

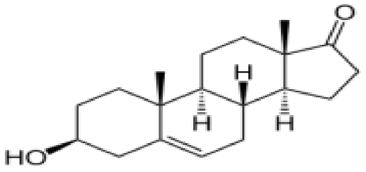
DEL-1 levels diminish in old age.

Is there a connection?

Perspective & therapeutic implications

- DEL-1 is expressed in the MSC niche of the periodontal ligament.
- Aging-related DEL-1 deficiency may contribute to stem cell niche dysfunction in the PDL.
- This in turn may contribute to defective osteogenesis and compromise periodontal tissue repair in old age.
- DEL-1-based strategies to improve bone regeneration in old age.
  - Exogenously administer recombinant DEL-1.
  - Stimulate endogenous DEL-1 expression in old age (DHEA, ERM).

Compounds shown to upregulate DEL-1 production



Dehydroepiandrosterone

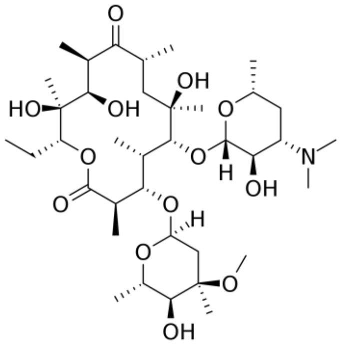
DHEA Inhibits Leukocyte Recruitment through Regulation of the Integrin Antagonist DEL-1

Athanasios Ziogas,[*,1] Tomoki Maekawa,[†,‡,1] Johannes R. Wiessner,[§] Thi Trang Le,* David Sprott,* Maria Troullinaki,* Ales Neuwirth,* Vasiliki Anastasopoulou,* Sylvia Grossklaus,* Kyoung-Jin Chung,* Markus Sperandio,[§] Triantafyllos Chavakis,[*,¶,2] George Hajishengallis,[†,2] and Vasileia Ismini Alexaki[*,2]

The Journal of Immunology, 2020, 204: 1214–1224.

JCI insight

2020;5(15):e136706.



Erythromycin

Erythromycin inhibits neutrophilic inflammation and mucosal disease by upregulating DEL-1

Tomoki Maekawa,[1,2,3] Hikaru Tamura,[1,2,3] Hisanori Domon,[1,2] Takumi Hiyoshi,[1,2] Toshihito Isono,[2] Daisuke Yonezawa,[1,4] Naoki Hayashi,[5] Naoki Takahashi,[3] Koichi Tabeta,[3] Takeyasu Maeda,[1,6] Masataka Oda,[5] Athanasios Ziogas,[7] Vasileia Ismini Alexaki,[7] Triantafyllos Chavakis,[7,8] Yutaka Terao,[1,2] and George Hajishengallis[9]

Acknowledgments

Hajishengallis lab

Penn Dental Medicine
Basic & Translational Sciences

Present and former members

Xiaofei Li
Dayo Yuh
Hui Wang
Tetsuhiro Kajikawa
Jong-Hyung Lim
Gundappa Saha
Tomoki Maekawa
Kosuke Nagai
Hidetaka Iguchi
Baomei Wang
Toshiharu Abe
Jieun Shin

Dept. of Biology
Xiang Yu

Dept. of Periodontology
Jonathan Korostoff

Dept. of Pathology and Laboratory Medicine
Khalil Bdeir

Collaborators

DEL-1/trained immunity/CHIP
Triantafyllos Chavakis (Dresden)
Lydia Kalafati (Dresden)
Ioannis Kourtzelis (Dresden)
Ioannis Mitroulis (Dresden)

Trained immunity
Mihai Netea (Nijmegen)

CHIP
Kimon Divaris (UNC)

Treg cells
Veronica de Rosa (Napoli)
Giuseppe Matarese (Napoli)

LAD/Th17
Niki Moutsopoulos (NIDCR)
Steven Holland (NIAID)

Complement
John Lambris (Penn)

Amyndas Pharmaceuticals
Despina Yancopoulou

Forsyth
Hatice Hasturk

SICONBREC (Philippines)
Ranillo R.G. Resuello
Joel V. Tuplano

Manila Central University
Ruel A. Briones
Cristina A.G. Garcia

Keystone pathogen / PSD model
Patricia Diaz (Buffalo)
Richard Lamont (Louisville)
Mike Curtis (London)
Richard Darveau (Seattle)

NIH National Institute of Dental and Craniofacial Research

National Institute of Allergy and Infectious Diseases