

The Bigger Picture: Why Oral Mucosa Heals Better Than Skin

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Table S1: Direct comparison between skin and oral wound healing in processes involved in the inflammatory phase

Inflammation phase	model			difference	(ref)
(2-72 hours)	species	stimulus	Time (h)		
Immune cells					
neutrophils (MPO)	Humans Mice	3 mm biopsy 1 mm biopsy	24-72 hours 3-6 days 2, 4, 12, 24, 48, 72 hours	More in oral More in skin More in skin	[36] [69]
Macrophages	Humans Pigs Mice	3 mm biopsy 15x27 mm excision 1 mm biopsy	24-72 hours 72 hours 14-60 days 2, 4, 12, 24, 48, 72 hours	More in skin More in oral More in skin More in skin	[36] [21] [21] [69]
T lymphocytes (CD3)	Humans Mice	3 mm biopsy 1 mm biopsy	24-72 hours 7 days	More in oral More in skin	[36] [69]
Mast cells	Rat	15x27 mm excision	72 hours	More in skin	[21]
Chemokines <i>in vivo</i>					
CCL2 (MCP-1)	Human	3mm biopsy	24-72 hours	More in skin	[36]
CCL3 (MIP-1a)	Human Mice	3mm biopsy 1mm biopsy	24-72 hours 0 ,6 ,12, 24, 72 hours	More in skin More in skin	[36] [73]
CCL5 (RANTES)	Mice	1mm biopsy	0 ,6 ,12, 24, 72 hours	More in oral	[73]
CCL20	Mice	1mm biopsy	0 ,6 ,12, 24, 72 hours	No difference	[73]
CCL27	Human	3mm biopsy	1, 3, 6 days	More in skin*	[36]
CXCL1 (GRO1/KC)	Human	3mm biopsy	72 hours	More in skin	[36]
CXCL2 (MIP-2a)	Human	3mm biopsy	24-72 hours	More in skin	[36]
CXCL5 (ENA-78)	Human	3mm biopsy	24-72 hours	More in skin	[36]
CXCL7 (NAP-2)	Mice	1mm biopsy	0, 6, 12, 24, 72 hours	More in skin	[73]
CXCL8 (IL-8)	Human Mice	3mm biopsy 1mm biopsy	24-72 hours 2, 4, 12, 24, 48, 72 hours	More in skin More in skin	[36] [69]
CXCL10	Human Mice	3mm biopsy 1mm biopsy	1-2-6 days 2, 4, 12, 24, 48, 72 hours	More in oral* More in skin*	[36] [73]

	model			difference	(ref)
Chemokines <i>in vitro</i>	species	stimulus	Time (h)		
CCL2 (MCP-1)	human tissue equivalent	TNF- α	24 hours	More in skin	[71]
	primary human keratinocytes	UVB	24 hours	No difference	[70]
		TNF- α / IFN- γ	8 hours	More in oral	[76]
	primary human fibroblasts	TNF- α	24-72 hours 24 hours	More in skin More in skin	[76] [71]
CCL3 (MIP-1a)	primary human keratinocytes	TNF- α / IFN- γ / IL-1 α /IL-4/ TGF- β	2, 4, 12, 24, 48, 72 hours	No difference	[72]
CCL5 (RANTES)	primary human keratinocytes	TNF- α / IFN- γ	24 hours	No difference	[72]
	primary human fibroblasts	TNF- α	24 hours	No difference	[71]
	human tissue equivalent	TNF- α	24 hours	No difference	[71]
		UVB		No difference	[70]
CCL20	primary human fibroblasts	TNF- α	24 hours	No difference	[71]
	human tissue equivalent	TNF- α	24 hours	More in skin*	[71]
CCL27	primary human keratinocytes	TNF- α	24 hours	More in skin	[71]
	human tissue equivalent	Baseline	24 hours	More in skin	[71]
CCL28	primary human keratinocytes	TNF- α	24 hours	More in oral	[71]
CXCL8 (IL-8)	primary human fibroblasts	TNF- α	24 hours	Same/oral?	[71]
	primary human keratinocytes	TNF- α / IFN- γ	2, 4, 12, 24, 48, 72 hours	More in oral	[72]
	human tissue equivalent	TNF- α	24 hours	No difference	[71]
		UVB	24 hours	More in oral	[70]
CXCL10	Human tissue equivalent	UVB	24 hours	More in oral	[70]
CXCL12 (SDF-1)	human tissue equivalent	TNF- α	24 hours	More in skin	[71]
	primary human fibroblasts	TNF- α	24 hours	More in skin	[71]
		baseline	7 days	More in skin	[83]
ICAM-1	primary human oral/skin keratinocytes	TNF- α / IFN- γ	24 hours	More in oral	[74]
Cytokines <i>in vivo</i>					
IL-6	Human	3mm biopsy	24-72 hours	More in skin*	[36]
	Mice	1mm biopsy	2, 4, 12, 24, 48, 72 hours	More in skin	[69]
IL-1 α	Human	3mm biopsy	24-72 hours	More in oral*	[36]

IL-1 β	Human	3mm biopsy	24-72 hours	More in oral (absolute) More in skin (increase)	[36]
IL-10	Mice	1 mm biopsy	2, 4, 12, 24, 48, 72 hours	No difference	[69]
IL-23	Mice	1 mm biopsy	0, 6, 12, 24, 48 hours	More in skin*	[73]
IL-24	Mice	1 mm biopsy	0, 6, 12, 24, 48 hours	More in skin*	[73]
IFN- α/β	Mice	1 mm biopsy	0, 6, 12, 24, 48 hours	More in skin*	[73]
G-CSF	Mice	1 mm biopsy	0, 6, 12, 24, 48 hours	More in skin*	[73]
Cytokines <i>in vitro</i>					
IL-6	human tissue equivalent	TNF- α	24 hours	No difference	[71]
	Primary human keratinocytes	UVB	24 hours	More in oral	[70]
		IL-1 β	0, 6, 12, 24, 48 hours	More in skin*	[73]
			24 hours	More in oral	[61]
		IFN- γ	24 hours	No difference	[61]
	Primary human fibroblasts	TNF- α	24 hours	More in oral	[61]
		IL-4	24 hours	More in oral	[61]
		TGF- β	24 hours	No difference	[61]
		CXCL8	24 hours	No difference	[61]
		TNF- α	24 hours	No difference	[71]
IL-1 α	Primary human keratinocytes	TNF- α	24 hours	No difference	[61, 71]
		TNF- α +IFN- γ	24 hours	No difference	[61]
IL-1 β	Human tissue equivalent	UVB	24 hours	More in oral	[70]
TNF- α	Human tissue equivalent	UVB	24 hours	More in oral	[70]
	Primary human keratinocytes	IL-1 β	2, 4, 12, 24, 48, 72 hours	More in skin*	[73]
IL-10	Human tissue equivalent	UVB	24 hours	No difference	[70]
IL-18	Human tissue equivalent	CA	24 hours	More in skin	[71]
	Primary human keratinocytes	TNF- α	24 hours	More in skin	[71]

*no direct comparison/statistics

Table S2: Direct comparison between skin and oral wound healing in processes involved in the proliferation phase

Proliferation phase (3-7 days)	model			Difference	Ref
	Species	stimulus	time		
Wound closure (macroscopic)	Human Pig Pig Rat	3-5 mm biopsy 2x12 mm excision 15x17 mm excision 4 mm biopsy	9-15 days 14-49 days 28-60 days 1-7 days	Faster in oral Faster in oral Faster in oral Faster in oral	[36] [95] [21] [59]
Wound re-epithelialization (histology)	Pig Pig Human Mouse	2x12 mm excision 15x17 mm excision 3-5 mm biopsy 1 mm biopsy	4 days 28 days 3-6 days 1-3 days	No difference No difference Faster in oral Faster in oral	[95] [21] [36] [69, 96]
Fibroblast migration	Primary human fibroblasts	Baseline	2 days 4 days	No difference Faster in oral	[117] [116]
Fibroblast proliferation	Primary human fibroblasts	Baseline 3D culture TGF- β 1	8 days 2 days 1-6 days 3-14 days 3-15 days 24 hours 24 hours	No difference No difference No difference Faster in oral Faster in oral No difference Increase in skin Decrease in oral	[116] [117] [119] [83] [115] [118] [125] [125]
Fibroblast contraction	Primary human fibroblasts	Baseline		More in oral	[103, 117, 127, 128]
α -SMA expression	Primary human fibroblasts	Baseline		More in skin More in oral	[103, 127] [117]
Fibroblast integrin expression	Primary human fibroblasts	Baseline		More in skin	[121]
Keratinocyte migration	Mouse/Human primary keratinocytes	Baseline		Faster in oral	[16]
Keratinocyte proliferation	Mouse/Human primary keratinocytes	Baseline		More in oral	[16, 115]
β 6 Integrin	Pig	2x12 mm excision	0, 3, 7, 14, 21, 35, 49 days	More in oral	[123]

Growth factors	model			Difference	Ref
<i>in vivo</i>	Species	stimulus	time		
TGF- β	Pig	15x17 mm excision	60	More in skin	[21]
TGF- β 1	Pig Mice	2x12 mm excision 1 mm biopsy	0, 3, 7, 14, 21, 35, 49 days 12, 24, 48 hours 12, 24, 48, 72 hours	No difference More in skin More in skin	[123] [96] [69]
TGF- β 3	Pig Mice	2x12 mm excision 1 mm biopsy	0, 3, 7, 14, 21, 35, 49 days 12, 24, 48 hours	More in skin No difference	[123] [96]
pSMAD	Pig	2x12 mm excision	Baseline 60 days	More in oral More in skin	[21] [21]
FGF2/bFGF	Mice Rat	1 mm biopsy 4 mm biopsy	1, 2, 3, 5, 7 days 0, 1, 2, 3, 4, 5 days	No difference More in oral	[19] [59]
VEGF	Mice Rat	1 mm biopsy 4 mm biopsy	1, 2, 3, 5, 7 days 0, 1, 2 days 4, 5 days	More in skin/no difference More in oral More in skin	[19] [59] [59]
PDGF	Rat	4 mm biopsy	0, 1, 2, 3, 6, 7 days	More in oral	[59]
EGF	Rat	4 mm biopsy	1, 2, 3, 4, 5, 6 days	More in oral	[59]
HIF-1 α	Mice	1 mm biopsy	6-24h	More in skin	[99]
Growth factors <i>in vitro</i>					
TGF- β 1	Primary human fibroblasts	3D culture	7 days	More in skin	[83]
TGF- β 2	Primary human fibroblasts	3D culture	7 days	More in oral	[83]
TGF- β 3	Primary human fibroblasts	3D culture	7 days	More in oral More in skin	[96] [83]
pSMAD	Primary human fibroblasts	3D culture	7 days	More in skin	[83]
FGF2	Primary human fibroblasts	3D culture	7 days	No difference	[83]
FGF7 (KGF)	Primary human fibroblasts	baseline	Baseline	More in oral	[103]
HGF	Primary human fibroblasts	baseline	Baseline	More in oral	[103]
KGF	Primary human fibroblasts	Baseline	Baseline	More in oral	[103]
VEGF- α	Primary human fibroblasts	3D culture	7 days	More in oral	[83]

Table S3: Direct comparison between skin and oral wound healing in processes involved in the remodeling phase

Remodeling	model			difference	(ref)
(days-weeks-months)	species	stimulus	Time (h)		
Scarring (macroscopically)	Pig	2x12 mm excision 15x27 mm excision	49 days 42, 46, 49 days 60 days	More in skin	[123] [95] [21]
Scarring (microscopically)	Pig	2x12 mm excision	49 days	More in skin	[95]
Contraction (macroscopically)	Pig	15x27 mm excision	60 days	More in skin	[21]
Epithelial thickness	Pig	15x27 mm excision	60 days	More in skin	[21]
Rete ridges	Pig	15x27 mm excision	60 days	More in oral	[21]
Cells					
Macrophages (CD169) (CD163) (CD86)	Pig Pig Human	1 mm biopsy 15x27 mm excision 1 mm biopsy	? 60 days 1-3-6 days	More in skin More in skin? More in skin?	[69] [21] [36]
Mast cells	Pigs	15x27 mm excision	60 days	More in skin	[21]
Myofibroblasts (a-SMA)	Pig Rat	15x27 mm excision Collagen implant	60 days 1-2-4-8-16 weeks	More in oral More in oral (1-2 weeks)	[21] [130]
Fibroblasts	Pigs	15x27 mm excision	60 days	More in skin	[21]
Blood vessels	Pig Rat	15x27 mm excision Collagen implant	60 days 1-2-4-8-16 weeks	No difference/ More in skin More in oral (1-2-4 weeks)	[21] [130]
Extracellular matrix <i>in vivo</i>					
Collagen density	Pig	15x27 mm excision	60 days	oral	[21]
Collagen maturity	Pig	15x27 mm excision	60 days	oral	[21]

Collagen fiber thickness	mice	1 mm biopsy	3-5-7-14 days	skin	[96]
Pro-collagen 1	Pig	2x12 mm excision	3-7-14-21-35-49 days	no difference/ skin	[95]
Fibronectin	Pig	2x12 mm excision	3-7-14-21-35-49 days	More in skin	[95]
Extracellular matrix in vitro					
Collagen 1 (mRNA)	Human fibroblasts	3D culture	1 week	More in skin	[83]
Collagen 1 (protein)		hypoxia	2 days	More in oral	[113]
			2 days	No difference	[113]
Collagen 3 (mRNA)	Human fibroblasts	3D culture	1 week	More in skin	[83]
Collagen 3 (protein)		hypoxia	2 days	More in skin	[113]
			2 days	More in skin	[113]
Elastin-1 (mRNA)	Human fibroblasts	3D culture	1 week	More in skin	[83]
Fibronectin - EDA - EDB	Human fibroblasts	3D culture	7 days	More in oral	[83]
				No difference	[83]
Emilin-1/-2 (mRNA)	Human fibroblasts	3D culture	1 week	No difference	[83]
Fibrillin-1 (mRNA)	Human fibroblasts	3D culture	1 week	No difference	[83]
SPARC-1 (mRNA)	Human fibroblasts	3D culture	1 week	More in skin	[83]
Tenascin-C (mRNA)	Human fibroblasts	3D culture	1 week	More in skin	[83]
Total MMP expression (mRNA)	Human fibroblasts	3D culture	1 week	More in oral	[83]
MMP1 (active)	Human tissue equivalent	3D culture	1, 2, 3 weeks	No difference	[136]
	Human fibroblasts	3D culture	1, 2, 3, 7, 14 days	No difference	[136]
			1 week	No difference	[83]
MMP1 (mRNA)	Human fibroblasts	3D culture	1 week	More in oral	[83]

MMP2 (active)	Human fibroblasts	3D culture, baseline	1, 2, 3 days	No difference	[128]
MMP2 (protein)	Human tissue equivalents	3D culture, baseline	1 week	More in oral	[128]
	Human fibroblasts	3D culture, baseline	1, 2, 3 weeks	No difference	[134]
			1, 2, 3 days, 1-6 weeks	No difference	[134]
			1, 2, 3, 7 days	No difference	[128]
MMP2 (mRNA)	Human fibroblasts	3D culture, baseline	1 week	No difference	[83, 128]
MMP3 (active)	Human fibroblasts	3D culture, baseline	2 days	More in oral	[127]
MMP3 (protein)			2 days	More in oral	[113, 127]
		hypoxia	2 days	More in oral	[113]
MMP3 (mRNA)		3D culture, baseline	1 day	More in oral	[127]
			1 week	More in oral	[83]
MMP7 (mRNA)	Human fibroblasts	3D culture	1 week	More in skin	[83]
MMP9 (active)	Human tissue equivalents	Baseline	1-4 weeks	More in skin*	[134]
	Human fibroblasts	3D culture	1, 2, 3, 7, 14 days	More in oral*	[134]
MMP9 (protein)	Human fibroblasts	3D culture	1, 2, 3, 7 days	More in oral*	[134]
MMP10 (active)	Human fibroblasts	3D culture	1 week	More in oral	[83]
MMP10 (protein)		3D culture	2 days	More in oral	[113]
		Hypoxia	2 days	More in oral	[113]
MMP10 (mRNA)	Human fibroblasts	3D culture	1 week	More in oral	[83]
MMP11 (mRNA)	Human fibroblasts	3D culture	1 week	More in skin	[83]
MMP12 (mRNA)	Human fibroblasts	3D culture	1 week	No difference	[83]
TIMP1 (active)	Human fibroblasts	3D culture	1 week	More in skin	[128]
TIMP1(mRNA)			1 day	No difference	[128]
			1 week	No difference	[83]
TIMP2 (active)	Human fibroblasts	3D culture	1 week	More in skin	[128]
TIMP2 (mRNA)			1 day	No difference	[128]
			1 week	No difference	[83]
TIMP3 (mRNA)	Human fibroblasts	3D culture	1 week	No difference	[83]
TIMP4 (mRNA)	Human fibroblasts	3D culture	1 week	More in oral	[83]

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