ANNNOTATED

HOMEOSTASIS BIBLIOGRAPHY

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Baggiolini, M, et al

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J. Exp. Med., 186(8) pg. 1189-1191, 1997

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Spilanthol: occurrence, extraction, chemistry and biological activities

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Spilanthol is found in many different plants around the world used as traditional remedies. Mouthwatering, antioxidant, analgesic, neuroprotective, anti-inflammatory and antimicrobial effects have been found.

Bayer

Dexpanthenol Clinical Study Synopsis - clinical trial - NCT00859196

Clinical trial of dexpanthenol on skin demonstrated wound healing and gene expression results consistent with beneficial wound healing.

Boonen, J., et al

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Journal of Ethnopharmacology, 127, pg 77-84, 2010

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IL-6-dependent PGE2 secretion by mesenchymal stem cells inhibits local inflammation in experimental arthritis

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Byun, J.Y., et al

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Resolution of inflammation is initiated by recognition of apoptotic cells. COX-2/PGE2 and HGF play important roles in tissue repair process.

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Antioxidants and redox signaling, 25(17), pg. 953-964, 2016

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Heise, R., et al

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Calcium ion is the most pervasive signaling molecule in living organisms. Positive and negative calcium effects on cAMP levels is found in every cell of every organ to control energy, immune response and homeostasis.

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Cellular Signaling, 15, pg. 299-306, 2003

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Cancer: A Cancer Journal for Clinicians, 51(5), pg 290-315, 2009

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Kota, D.J., et al

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Stem Cells, 35, pg 1416-1430, 2017

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Li, Y., et al

CXCL12-engineered endothelial progenitor cells enhance neurogenesis and angiogenesis after ischemic brain injury in mice

Stem Cell Research & Therapy, 2018, DOI:10.1186/s13287-018-0865-6 , 15pages

Ischemic strokes cause brain damage. CXCL12, a chemoattractant for stem cells, has been shown to improve angiogenesis, neurogenesis and remyelination acting through epithelial progenitor cells. Agents improving this attraction may give improved recovery of strokes.

Li, M., et al

SDF-1/CXCR4 axis induces human dental pulp stem cell migration through FAK/PI3K/AKT and GSK2b/b-catenin pathways

Scientific Reports, 2017, DOI:10.1038/srep40161 13 pages

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better protection of tissue ischemia.

Li, X., et al

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PLOS One, 11(10):e0163807, 2016 14 pages

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The molecular basis of JAK/STAT inhibition by SOCS1

Nature Communications 9, pg. 1558, 2018

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TGF-beta increases ROS and decreases glutathione in fibrotic diseases. Agents decreasing TGF-beta and increasing glutathione may help reverse fibrosis.

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JBC, 282, pg. 29470-29481, 2007

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Cannabinoid-based drugs targeting CB1 and TRPV1, the sympathetic nervous system, and arthritis

Arthritis Research & Therapy, vol 17, pg 226, 2015

Chronic inflammation in rheumatoid arthritis activates sympathetic nervous system which supports immune system to perpetuate inflammation. WhiteHill case study positive result on RA patient is consistent with TRPV1 action of homeostasis synergetic agents

Lu, X., et al

PGE2 promotes the migration of mesenchymal stem cells through the activation of FAK and ERK1/2 pathway

Stem Cells International, 2017, DOI:10.1155/2017/8178643 - 11 pages

PGE2 used in MSC multiplication gives enhanced migration ability to the wounded site by effecting the EP2 receptors and activating the FAK and ERK1/2 pathways.

Marshall, C., et al

Cutaneous scarring: Basic science, current treatments, and future directions

Advances In Wound Care, 7(2), pg 29-45, 2018

Scars as a result of surgery, burns or injury constitute a major burden on the healthcare system. Recent discoveries have clarified the role of skin stem cells and fibroblasts in regeneration of injuries and in scarring.

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MSC are currently being investigated in numerous clinical trials of tissue repair and in immune disorders. MSC migrate to the site of insult in response to chemokines such as SDF-1(CXCL12). Increasing expression of the receptor CXCR4 would help the migration become more efficient.

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Dermatopathology, 1, pg. 98-107, 2014
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COX-2 is a target for new drug development in cancer therapy in cancer stem cell delayed activity.

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The genus Spilanthes ethnopharmacology, phytochemistry and pharmacological properties: a review
Advances in Pharmacological Sciences, 2013, DOI:10.1155/2013/510298 22 pg
Spilanthes spp. are popular over the counter remedies use in traditional medicines

used for pain, gum infections periodontosis and swelling and used orally or topically.

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The role of the TGF-b family in wound healing, burns and scarring: a review

Int. J. Burn Trama, 2(1), pg 18-28, 2012

Approximately 6 million people experience a burn per annum. Scarring is a heavy burden to overcome and it controlled by TGF-beta isoforms 1,2 and 3. Altering the ratios of these will give scarless healing.

Qin, C.X., et al

Endogenous annexin-a1 regulates haematopoietic stem cell mobilization and inflammatory response post myocardial infarction in mice in vivo

Science reports, 2017 DOI:10.1038/s41598-017-16317-1 14 pages

Endogenous annexin A1 plays an important role in preserving heart function after a stroke. Loss of annexin A1 gives exaggerated inflammation. Genetically altered mice without annexin A1 gave increased infarction size

Rackham, C.I., et al

Annexin A1 is a key modulator of mesenchymal stromal cell-mediated improvements in islet function

Diabetes, 65: pg 129-139, 2016

MSC may improve diabetic treatments in islet cell transplantation.

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Innate immunity derived factors as external modulators of the CXCL12-CXCR4 axis and their role in stem cell homing and mobilization

Theranostics,, 3(1), pg. 3-10, 2013

CXCL12 is a chemoattractant for MSC and is important is stem cell homing after transplantation.

Reid, J.C., et al

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Stem Cell Reports, 10, pg. 1625-1641, 2018

Test results show that CXCR4 should be addressed to generate MSC successful for transplantation.

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The Cannabinoid Receptor Type 2 as Mediator of Mesenchymal Stromal Cell Immunosuppressive Properties.

PLOS ONE, Vol. 8, Issue 11, Nov. 2013, e80022

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Densitization of Transient Receptor Potential Ankyrin 1 (TRPA1) by the TRP vanilloid 1-sellective cannabinoid Arachidonoyl-2 Chloroethanolamine

Mol. Pharmacol. 2011, vol. 80(1), pg 117-123

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TGF-b family signaling in stem cells

Biochimica et Biohysica Acta, 1830, pg. 2280-2296, 2013

These studies gave a better understanding of how TGF-beta regulates stem cells

Santibanez, J.F., et al

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BioMol Concepts, 3, pg. 429-445, 2012
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Cold Spring Harbor Perspectives in Biology, DOI:10.1101/cshperspect.a016311
21 pages
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Phytomedicine, 18, pg. 1161-1169, 2011
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The physiology of wound healing
Surgery, 35(9), pg. 473-477, 2017
Wounding healing is a complex and time differentiated process. Inflammation, proliferation and tissue remodeling are important steps for healing in a homeostatic manner.

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Pantothenic acid and pantothenol increase biosynthesis of glutathione by boosting cell energetics
FEBS letters, 569, pg. 169-172, 2004
Human lymphoblastic cells increase glutathione content under the agency of pantothenate, dexpanthenol. This was due to increase production of ATP and mitochondrial CoA.

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Effect of **spilanthes** acmella hydrothanolic extract activity on the tumour cell actin cytoskeleton
Cell Biology Int. 38, pg. 131-135, 2014
Spilanthes extract demonstrated toxicity to cancer cells at 500 ug/mL.

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Prevention of chemotherapy-induced ulcerative mucositis by transforming growth factor beta3
Cancer Research, 54, pg. 1135-1138, 1994
Mucositis as result of chemotherapy or radiation therapy limits the treatment levels due to painful side effects in the oral cavity. Topical administration of TGF-beta3 gave reduced lesions in the oral cavity, increased feeding and improved weight gain in Syrian Golden Hamsters.

Spiegeleer, B., et al
Skin penetration enhancing properties of the plant N-alkylamide spilanthol
Journal of Ethnopharmacology, 148, pg. 117-125, 2013
The dermal penetration of caffeine and testosterone were improved 4 fold under the influence of spilanthol.

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Role of the CXCR4/SDF-1 chemokine axis in circulating neutrophil homeostasis
Blood, 104(2), pg. 565-571, 2004
The SDF-1/CXCR4 axis is crucial in maintaining a neutrophil level in the normal homeostatic range.

Veryser, L., et al

Mucosal and blood-brain barrier transport kinetics of the plant alkylamide spilanthol using in vitro and in vivo models

BMC complementary and alternative med, DOI:10.1186/s12906-016-1159-0
12 pages

The ability for spilanthol to penetrate the skin and subsequently the blood brain barrier is demonstrate using CACO-2 cells and in mice. Spilanthol rate of penetration is greater into the brain than the exit rate.

Veryser, L., et al

N-alkylamides: from plant to brain

Functional foods in health and disease, 4(6), pg. 264-275, 2014

Plant N-alkylamides are bio-active with broad functional spectrum. Kinetics of dermal, circulatory and brain penetration suggest they may be active in the brain.

Wang, L., et al

Exosomes secreted by human adipose mesenchymal stem cells promot scarless cutaneous repair by regulating extracellular matrix remodeling

Scientific Reports, DOI:10.1038/s41598-017-12919-x 2017

Scar formation is an intractable medical problem. Recent research hows stem cells secrete an agent that benefits wound healing. Exosome treatment down-regulated TGF-b1 and improved the TGF-b1/TGFb3 ratio leading to a high ratio of MMP3 to tissue inhibitors of MMP(TIMP1).

Wang, X., et al

Stem cell autocrine CXCL12/CXCR4 stimulates invasion and metastasis of esophageal cancer

Oncotarget, 8(22), pg. 36149-36160, 2017

Extracellular matrix is controlled by CXCL12/CXCR4 system to give a gain or loss of function through the ERK 1 and 2. Blocking of ERK may slow cancer development.

Watabe, T., et al

Roles of TGF-b family signaling in stem cell renewal and differentiation

Cell Research, 19, pg. 103-115, 2009

TGF-beta control development and maintenance of various organs. Stem cell differentiation into myofibroblasts point to possible scarring

Waterman, R.S., et al

A new mesenchymal stem cell(MSC) paradigm: Polarization into a pro-inflammatory MSC1 or and immunosuppressive MSC2 phenotype

PLOS One, 5(4), e10088, 2010 - 14 pages

Mesenchymal stromal cells can point to inflammation by action of TLR agents. TLR4 gives an inflammatory MSC, while TLR3 gave immunosuppressive action.

Weber, C. E., et al

Epithelial-mesenchymal transition, TGF-b and Osteopontin in wound healing and tissue remodeling after injury

J. Burn Care Res. 33(3), pg. 311-318, 2012

Epithelial to mesenchymal transition is essential to development and to wound healing. The time-line of healing is mediated by the differentiating aspect of local cells. Osteopontin and TGF-beta are controlling the differentiation called EMT.

Werner, L., et al

Involvement of CXCR4/CXCR7/CXCL12 interactions in inflammatory bowel disease

Theranostics, 3(1), pg. 40-46, 2013

The CXCR4 and its ligand CXCL12 act in the progress of inflammation and the migration of immune cells to the endpoint of homeostasis. Inflammatory bowel disease is controlled by the cytokines along with CXCR7.

Weiderholt, T., et al

Calcium pantothenate modulates gene expression in proliferating human dermal fibroblasts

Experimental Dermatology, 18, pg.969-978, 2009

Pantothenate and dexpanthenol enhance migration and proliferation o fibroblasts to the wound site. Genes involved are IL-6,. IL-8, HO-1, CYP1B1 and HspB7.

Wong, V.W., et al

Focal adhesion kinase links mechanical force to skin fibrosis via inflammatory signaling

Nature Medicine, 18(1), 148-154, 2012

Healing of wounds are found in these experiments to involve mechanical action which is expressed int the upregulation of FAK/ERK/MCP1

Woods, L.T., et al

Increased expression of TGF-b signaling components in a mouse model of fibrosis induced by submandibular gland duct ligation

PLOS One, 2015, DOI:10.1371/journal.pone.0123641 - 24 pages

Signals of fibrosis such as E-cadherin, collagen 1 and fibronectin were upregulated in scarring. Blockage of TGF receptors by inhibitors gave reduced scarring and fibrosis.

Wu, L., et al

Anti-inflammatory effect of spilanthol from Spilanthes acmella on murine macrophage by down-regulating LPS-induced inflammatory mediators

J. Agric. Food Chem. 56, pg 2341-2349, 2008

The purification and biological activity were explored on murine RAW 264.7 macrophage cells. Inflammatory markers such as iNOS, COX2 and NFkB were down-regulated by purified spilanthol in these murine cells.

Wu, Q., et al

Extracellular calcium increases CXCR4 expression on bone marrow-derived cells and enhances pro-angiogenesis therapy

Molecular Medicine, 13(9B), pg. 3764-3773

Calcium control of expression of cell surface receptor CXCR4 was demonstrated while CXCL12 was controlled by bone marrow cells (BMC). Thus, calcium is a positive regulator of stem cell mobilization, homing and therapy.

Xiao, H., et al

Metformin is a novel suppressor for transforming growth factor (TGF)-b1

Science Reports, 2016, DOI:10.1038/srep28597 - 9 pages

TGF-beta is a source of pathogenesis of numerous diseases and is a target of metformin. The results are that TGF-beta dimerization is blocked by metformin and this should have therapeutic potential in a number of diseases where TGF-beta1 hyperfunction is indicated.

Xinaris, C., et al

A novel strategy to enhance mesenchymal stem cell migration capacity and promote tissue repair in an injury specific fashion

Cell Transplantation, 22, pg. 423-436, 2013

IGF-1 improves migration and homing capacity of MSC and is possibly rational approach to organ repair.

Xu, C., et al

Oxidative stress induces stem cell proliferation via TRPA1/RYR-mediated Ca2+ signaling in the drosophila midgut

eLIFE, 2017, DOI:10.7554/elife.22441 - 24 pages

Oxidative stress such as ROS triggers stem cell proliferation to restore homeostasis.

Yang, D., et al

Stromal Cell-derived Factor-1 receptor CXCR4-overexpressing bone marrow mesenchymal stem cells accelerate wound healing by migration into skin injury areas

Cellular Reprogramming, vol 15(3), pg. 206-215, 2015

Stromal cell-derived factor -1 and its membrane receptor CXCR4 are involved int homing and migration of stem cells to speed wound healing.

Yang, J.X., et al

CXCR4 receptor overexpression in mesenchymal stem cells facilitates treatment of acute lung injury in rats

JBC, 290(4), pg. 1994-2006, 2015

The CXCR4 receptor is experimentally overexpressed in MSC to reduce fibrotic lung injury.

Zeng, Y., et al

Role of the stromal cell derived factor-1CXC chemokine receptor 4 axis in the invasion and metastasis of lung cnacer and mechanism

Journal of Thoracic Disease, 9(12), pg. 4947-4959, 2017

Enhanced CXCR4 in cancer cells correlates with more vigorous metastatic action. Blockage of CXCR4 may give a cancer control point.

Zhang, C., et al

Cytokines regulating hematopoietic stem cell function

Curr. Opin. Hematol, 15(4), pg. 307-311, 2008

Review of stem cell experiments in genetic manipulation gives incite into the control points for stem cells.

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CXCR4/CXCL12 axis counteracts hematopoietic stem cell exhaustion through selective protection against oxidative stress

Scientific Reports, 2016, DOI:10.1038/spre37827 - 13 pages

Expression of CXCR4 and CXCL12 acting by ROS blocks stem cell exhaustion. CXCL12 rescues stem cells form oxidative stress.

Zhao, J., et al

Prostaglandin E2 inhibits collagen synthesis in derma fibroblasts and prevents hypertrophic scar formation in vivo

Experimental Dermatology, 25, pg. 604-610, 2016

The anti-scar effect of PGE2 is acting by upregulating cAMP thought the EP2 receptor. Scar reduction is achieved through balancing the MMP/TMP expression and thus

decreasing collagen.