

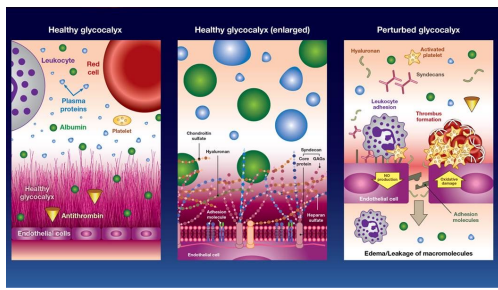
### Why Venous Leg Ulcer Have Difficulty Healing

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### Disclosures

Nothing to Disclose  
 No Other Conflicts of Interest



Courtesy of Dr. Scott M. Smith  
 Biomedical Research and Environmental Sciences Division (SEK)  
 NASA Johnson Space Center

C2-C5 CVD pt vs. ctrl EC  
 Primary disease all SVI

Endothelial Cells Obtained from Patients Affected by Chronic Venous Disease Exhibit a Pro-Inflammatory Phenotype

Control  
 -Decreasing shear stress  
 -Increasing inflammation

C4

- RBC and plaques (\*) attached to EC, and microvilli (↑)
- Disorganized, irregular orientation and discontinuous EC (Δ)
- Increased with C class

Tsisto V. et al Plos One 2012;7:1-13.

### Vascular pathologies and inflammation: the anti-inflammatory properties of sulodexide

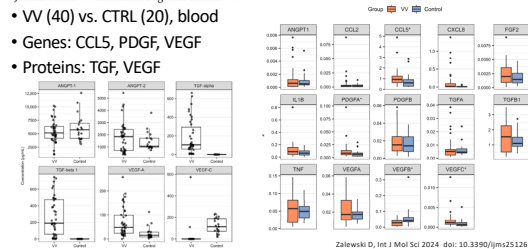
Activities	Experimental System	Reference
<b>Stimulatory action</b>		
Increase of heparan-sulfate (HS) expression and block of the HS decrease from cell surfaces	In vitro	Masola V 2011, <sup>17</sup> Rao G 2011 <sup>18</sup>
Increase of Superoxide-dismutase (SOD) activity	In vivo (mouse)	Jin HV 2011 <sup>22</sup>
Increase of hepatocyte growth factor (HGF) expression	In vivo (human)	Borawski J 2007 <sup>26</sup>
Increase of fibroblast growth factor (FGF-1) and FGF-2) mitogenic activity and prevent their proteolysis	In vitro	Tardieu M 1994 <sup>27</sup>
<b>Suppressive Action</b>		
Decrease of reactive oxygen species release	In vitro	Ciszewicz M 2009 <sup>21</sup>
Inhibition of glomerular heparanase-1 activity (HPSE)	In vitro	Masola V 2011, <sup>17</sup> Xu X 2005 <sup>19</sup>
Decrease of matrix metalloproteinase MMP-9 expression and activity	In vitro	Mannello F 2011, <sup>13</sup>
Decrease of Monocyte Chemoattractant Protein MCP-1 release	In vitro	Mannello F 2012, <sup>20</sup> Suninska-Jasinska K 2011, <sup>23</sup> Ciszewicz M 2009 <sup>21</sup>
Decrease of vascular endothelial growth factor VEGF activity	In vivo (mouse)	Pletnick A 2011 <sup>28</sup>
Decreased of transforming growth factor (TGFβ) expression	In vivo (human)	Masola V 2011, <sup>17</sup> Xu X 2005 <sup>19</sup>
Decreased of tumor necrosis factor TNFα expression	In vivo (mouse)	Karon J 2007 <sup>24</sup>
Decreased of interleukin 6 (IL6) release	In vitro/ in vivo (human)	Ciszewicz M 2009 <sup>21</sup>
Decreased of interleukin 8 (IL8) release	In vivo (human)	Fracasso A 2003 <sup>25</sup>
Decreased of interleukin E-1β (IL1β) release	In vivo (human)	Fracasso A 2003 <sup>25</sup>
Decreased of C-reactive protein (CRP) activity	In vivo (mouse)	Lauer DA 2005 <sup>16</sup>

Mattana P et al J Vasc Endovasc Surg 2012;19:1-7.

### Key Regulators of Angiogenesis and Inflammation Are Dysregulated in Patients with Varicose Veins

Daniel Zalewski<sup>1,4</sup>, Paulina Chmiel<sup>1,5</sup>, Przemyslaw Kolodziej<sup>2,6</sup>, Marcin Kocki<sup>3</sup>, Marcin Felde<sup>4,1</sup>, Janusz Kocki<sup>4,6</sup> and Anna Bogucka-Kocka<sup>1,4</sup>

- VV (40) vs. CTRL (20), blood
- Genes: CCL5, PDGF, VEGF
- Proteins: TGF, VEGF



Chronic venous disease – Part I: Inflammatory biomarkers in wound healing  
 Daniela Ligi<sup>1</sup>, Giovanni Mosti<sup>2</sup>, Lidia Croce<sup>3</sup>, Joseph D. Raffetto<sup>4,5</sup>, Ferdinando Mannello<sup>4,6</sup>  
 Chronic venous disease – Part II: Proteolytic biomarkers in wound healing  
 Daniela Ligi<sup>1</sup>, Giovanni Mosti<sup>2</sup>, Lidia Croce<sup>3</sup>, Joseph D. Raffetto<sup>4,5</sup>, Ferdinando Mannello<sup>4,6</sup>

**INFLAMMATORY PHASE**  
 IL-1 $\beta$ , IL-12, IL-8  
 IL-10, GM-CSF, VEGF  
 MMP-2, MMP-9, MMP-12  
 TIMP-1, TIMP-2

**GRANULATING PHASE**  
 IP-10, RANTES, PDGF $\beta$   
 MMP-1, MMP-7, MMP-13  
 TIMP-4

Courtesy of Professor Ferdinando Mannello  
 Ligi D et al Biochim Biophys Acta. 2016;1862:1964-74.  
 Ligi D et al Biochim Biophys Acta. 2016;1862:1900-8.  
 Ligi D et al Int J Mol Sci 2017;18:2206.

Iron and iron-dependent reactive oxygen species in the regulation of macrophages and fibroblasts in non-healing chronic wounds  
 Meitshard Wlaschek<sup>1</sup>, Karmveer Singh, Anca Sindrilari, Diana Crisan, Karin Scharfetter-Kochanek  
 Department of Dermatology and Allergy, Division, Otto University, 80001 Ulm, Germany

Wlaschek M et al Free Rad Biol Med 2019;133:262-275.

**Hemosiderin Deposition Containing Ferric Ions in VLU**

VLU border, excessive iron overload

Caggiati A et al EIMES 2010;40:777-82.

**Oxidation and Nitration**

- Reactive oxygen species (ROS)
- Reactive nitrogen species (RNS)
- Proteins → protein carbonylation
- Lipids → lipid peroxidation
- DNA → oxidation/nitration ONOO, SSB, PAR/PARP

Dodnar E et al Oxid Med Cell Longev 2018;5286785.

Redox Profiling Reveals Clear Differences between Molecular Patterns of Wound Fluids from Acute and Chronic Wounds  
 Edina Budnar,<sup>1</sup> Edina Bukondi,<sup>2</sup> Katalin Kovacs,<sup>3</sup> Csaba Hegedus,<sup>3</sup> Petra Lakatos,<sup>2</sup> Agneska Robaskiewicz,<sup>2</sup> Zsolt Regdon,<sup>2</sup> László Virág,<sup>1,2</sup> and Eva Szabó<sup>1</sup>

- Elevated LDH, IL-8, VEGF, TNF- $\alpha$ , lipid pox, GSH, Radical Scavenging Activity

In VLU fluid tissue biopsies:  
 - $\uparrow$ Antioxidant profiles and inflammation  
 -Elevated PAR (PARP, DNA damage/repair)  
 -Elevated Nitrotyrosine (ONOO)

Dodnar E et al Oxid Med Cell Longev 2018;5286785.

Predisposition, family history, genetics, environment → Macrovenous hemodynamic and microvenous endothelial and cellular changes

Venous valve dysfunction, reflux, obstruction → Venous Hypertension

Altered Shear Stress on Endothelium → GAG Glycoalyx Disruption on Endothelium

↑MCP-1, MIP-1, ↑ICAM-1, ↑VCAM-1, ↑NO, Selectins

↑Fe<sup>2+</sup>/Fe<sup>3+</sup>, ↑ROS, NOS, ↑Connexins, ↑TAM, TLR

Inflammatory Cell Infiltrate: MP, MC, TL

Wall/Valve/Tissue Cell Structural Functional change, Metabolic changes

MMPs Dilation/Remodeling and Tissue Injury, VV, skin changes, and VLU