DELAYED WOUND HEALING AND HYPERGRANULATION IN A CHILD WITH SMOC1 MUTATION: A CASE REPORT

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Background

Genetic mutations affecting critical molecular pathways can disrupt the process of wound healing, leading to complications such as delayed healing or hypergranulation tissue formation. SMOC1, a matricellular protein involved in various biological functions, has been implicated in platelet aggregation and endothelial cell activity, both of which are vital for effective wound repair. This case report explores the impact of a SMOC1 variant on wound healing in a pediatric patient, and a literature review provided mechanistic insights into the delayed healing observed.

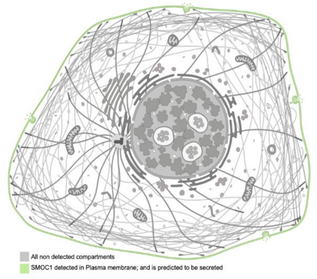
Methods

The healing trajectory of a 5-year-old female with a homozygous SMOC1 genetic variant was monitored following major surgery. Clinical observations, including time to healing and tissue morphology, were analyzed. Then, a comprehensive review of the scientific literature on SMOC1 function was evaluated to contextualize the observed clinical outcomes.

Wound Healing Clinical Observations

Clinical recovery was monitored by Dr. Kristin Weaver at Children's of Mississippi, University of Mississippi Medical Center, Jackson, MS, USA who commented that this healing process took approximately 4 times the duration for a typical recovery of this nature.

Importantly, it appears that there is a severity and/or depth requirement to enter into a regime in which SMOC1 dysfunction seems to be associated with such altered wound healing. The same individual had previously had a small incision in the groin region for catheter insertion for an ASD which healed quickly. While we do not know what the impact of sex or genetic background would be, specifically, different individuals with SMOC1 Related Dysfunction present differently. A different female child with a homozygous premature stop variant on her SMOC1 gene has yet to experience a surgery of the same nature as the one described above, however she did have a hernia with no apparent delay in healing (perhaps even accelerated). Her brother, also with the same homozygous variant on the SMOC1 gene experience prolonged bleeding in a recent hospitalization.



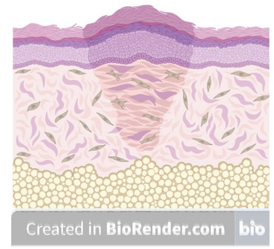
Literature Review

Searching for "smoc1" in pubmed and its ortholog in the flybase database, approximately 200 entries were discovered. All titles were reviewed finding only one that specifically referred to wound healing. Through evaluating abstracts, several more were determined to be related to wound healing. For a systematic approach, pubmed was searched using the query: "SMOC1" OR "Magu" OR "Pent" AND Wound, which resulted in 51 results. 47 of these were easily ruled out due to obvious reasons such as the abstract being on a separate topic with one of the authors' last names being Pent or Magu. The 4 identified systematically have bolded PMIDs and several others were identified through more manual methods.

PMID	Title	Findings and Implications	Comments
25902518	During Drosophila disc regeneration, JAK/STAT coordinates cell proliferation with Dilp8-mediated developmental delay	• Transcriptome analysis 24hrs after wounding revealed upregulated JAK signalling and reduced pent (smoc1 fly ortholog) expression.	Wound → ⬆️JAK, ⬇️SMOC1
32206122	Fasting before or after wound injury accelerates wound healing through the activation of pro-angiogenic SMOC1 and SCG2.	• Actually published afterwards, and inspired by a different set of scientific questions, this paper ended up reproducing several key findings from PMID 25750188. • Specifically, that reducing SMOC1 expression results in reduced proliferation and migration of endothelial cells (specifically they used human vascular endothelial cells).	⬇️SMOC1, ⬇️EC migration, and ⬇️EC proliferation
26265132	Integrated analyses of zebrafish miRNA and mRNA expression profiles identify miR-29b and miR-223 as potential regulators of optic nerve regeneration.	• The microRNA miR-223 was increased after damage to the zebrafish optic nerve. • SMOC1 was down-regulated at the same time point (3 days post-injury).	In what other contexts is miR-223 increased or decreased? See below re: platelets
38023706	Role of human dural fibroblasts in the angiogenic responses of human endothelial cells: An in vitro dural model and the application of lab-on-a-chip for EDAS.	• Role of IL-1β in stimulating SMOC1 expression and in increasingly levels more than 2FC. • Enhanced angiogenic response. • Increased migratory behavior of endothelial cells.	⬆️IL-1β, ⬆️SMOC1, ⬆️Angiogenesis, ⬆️EC migration
25750188	Role of secreted modular calcium-binding protein 1 (SMOC1) in transforming growth factor β signalling and angiogenesis	• IL-1β, TNF-α, TGFβ1, and conditions of hypoxia, all ⬆️SMOC1 (levels or expression) • miR-223 negatively regulates SMOC1 • SMOC1 co-localizes with endoglin	⬇️SMOC1, ⬇️EC migration, ⬇️ EC proliferation, altered tube formation
33529332	Secreted modular calcium-binding protein 1 binds and activates thrombin to account for platelet hyperreactivity in diabetes	• Since platelets are rich in miR-223, these authors studied SMOC1 expression in relation to platelet activity. • SMOC1 interacts directly with thrombin and increases platelet aggregation	⬇️SMOC1, ⬇️thrombin activity, ⬇️platelet aggregation
37445780	Systemic Review of Clot Retraction Modulators.	• Reviewed above paper and cited the lower clot retraction, platelet aggregation, platelet spreading, leukocyte–platelet aggregations, and thrombin-induced calcium mobilization in SMOC1 heterozygous mice.	See above
SMOC1 and SMOC2 are often referred to as SPARC-Related Modular Calcium-Binding Proteins 1 or 2. We examine several papers regarding SMOC2 and SPARC's relation to wound healing:			
18582461	The widely expressed extracellular matrix protein SMOC-2 promotes keratinocyte attachment and migration	• Similar to SMOC1, this paper describes SMOC2 as interacting with integrins. • Extracellular calcium binding domain involved with cell attachment and focal adhesion formation.	⬆️SMOC2, ⬆️migration • SMOC2 stimulates migration (but not proliferation) of keratinocyte-like cells
11532190	Impaired wound healing in mice deficient in a matricellular protein SPARC (osteonectin, BM-40)	• 25mm oblong full thickness incisions including the striated muscle layer (panniculus carnosus) were made in WT and SPARC null mice. • Impeded healing in null mice was attributed to poor migration (as opposed to proliferation) and they suggest this relates to dermal fibroblasts failing to disassemble cell-cell contacts.	⬇️SMOC1, ⬇️migration, • Smaller 6mm full-thickness incisions were made and gross appearance of wounds were similar bt WT/null. Why?
11748289	SPARC-null mice exhibit accelerated cutaneous wound closure	• 5mm punch biopsy wounds healed faster in SPARC null mice compared to WT • Collagen concentration lower in null, thought to enhance contractability	• Could this same decrease in collagen conc. be problematic in a larger wound?

The function of SMOC1 in the context of Wound Healing

From the information in the literature and from this case study showing wound healing delayed by a factor of four, we hypothesize that the reduction of loss of functional SMOC1 protein results in a dramatically reduced ability of deep wounds to progress to the proliferation stage.



Possibly the most directly relevant observation is shown below where knockdown of SMOC1 caused reduced migration of endothelial cells on both laminin and collagen substrates and, reduced proliferation as evidenced by time to confluency, and altered tube formation.

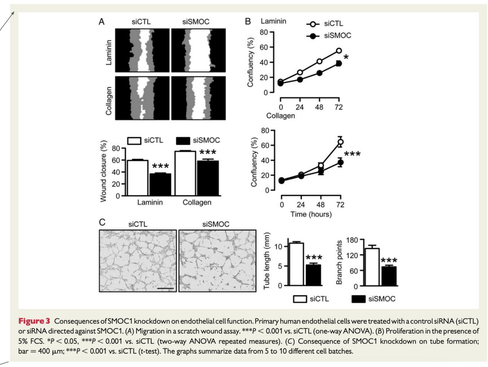


Figure 3 Consequences of SMOC1 knockdown on endothelial cell function. Primary human endothelial cells were treated with a control siRNA (siCTL) or siRNA directed against SMOC1. (A) Migration in a scratch wound assay. ***$P < 0.001$ vs. siCTL (one-way ANOVA). (B) Proliferation in the presence of 5% FCS. *$P < 0.05$, ***$P < 0.001$ vs. siCTL (two-way ANOVA repeated measures). (C) Consequence of SMOC1 knockdown on tube formation; bar = 400 μm; ***$P < 0.001$ vs. siCTL (*t*-test). The graphs summarize data from 5 to 10 different cell batches.

Results

The patient exhibited delayed wound healing, requiring approximately four times the expected duration to heal, alongside hypergranulation tissue formation. These clinical features suggest an arrest in the inflammatory phase and a failure to transition effectively to the proliferative phase. A review of the scientific literature on SMOC1 function identified one study detailing its role in platelet aggregation and two main studies examining the effects of SMOC1 knockdown on endothelial cells. The platelet aggregation study demonstrated that smoc1$^{+/-}$ mice exhibited reduced aggregation in response to low thrombin activity, likely impairing the first phase of repair. Platelet aggregation is critical for both hemostasis and the formation of a preliminary wound matrix, which serves as the foundation for subsequent stages of healing. The endothelial cell studies provided further insights, revealing that SMOC1 knockdown led to reduced proliferative and migratory capacity, as well as alterations in tube formation, indicative of impaired angiogenesis. Angiogenesis is a pivotal process for transitioning from the inflammatory to the proliferative phase of wound healing.

Conclusions

If the findings from these in vitro studies translate to the clinical context, it is reasonable to hypothesize that delayed wound healing in this patient was driven by defective provisional wound matrix and angiogenesis, which would implicate in impaired epithelial cell growth and migration. Together, these deficiencies likely arrest wound healing in inflammation and delay progression through proliferation. The observed hypergranulation tissue formation in the young female with a SMOC1 mutation aligns with these conclusions. Further studies are necessary to determine the relative contributions of these factors and validate their roles in SMOC1-related wound healing impairments.