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IP-10 induces dissociation of newly formed blood vessels

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Summary

The signals that prune the exuberant vascular growth of tissue repair are still ill defined. We demonstrate that activation of CXC chemokine receptor 3 (CXCR3) mediates the regression of newly formed blood vessels. We present evidence that CXCR3 is expressed on newly formed vessels *in vivo* and *in vitro*. CXCR3 is expressed on vessels at days 7–21 post-wounding, and is undetectable in unwounded or healed skin. Treatment of endothelial cords with CXCL10 (IP-10), a CXCR3 ligand present during the resolving phase of wounds, either *in vitro* or *in vivo* caused dissociation even in the presence of angiogenic factors. Consistent with this, mice lacking CXCR3 express a greater number of vessels in wound tissue compared to wild-type mice. We then hypothesized that signaling from CXCR3 not only limits angiogenesis, but also compromises vessel

integrity to induce regression. We found that activation of CXCR3 triggers μ -calpain activity, causing cleavage of the cytoplasmic tail of β 3 integrins at the calpain cleavage sites c'754 and c'747. IP-10 stimulation also activated caspase 3, blockage of which prevented cell death but not cord dissociation. This is the first direct evidence for an extracellular signaling mechanism through CXCR3 that causes the dissociation of newly formed blood vessels followed by cell death.

Supplementary material available online at
<http://jcs.biologists.org/cgi/content/full/122/12/2064/DC1>

Key words: Wound healing, Angiogenesis, Chemokines, Endothelial cells, Integrin

Introduction

Regulation of the vascular tree is critical to organogenesis and the 'neo-organogenesis' that occurs during wound repair. While many of the factors that initiate vascular growth are known, little has been deciphered about those that lead to subsequent involution or regression. Three possibilities, none mutually exclusive, have been forwarded: 'disuse atrophy' from mechanical factors secondary to decreasing metabolic load, decrease in pro-angiogenic factors, and actual pro-involution signals (Davis and Saunders, 2006; Lobov et al., 2005; Nyberg et al., 2005). This last possibility has been the least probed. Here, we propose that CXC chemokine receptor 3 (CXCR3) ligands serve as active signalers of vascular regression, at least during skin wound repair.

Early in the dermal wound healing process, the generation of new blood vessels is required for the regeneration of tissue. However, during the regenerative phase of wound healing, angiogenesis stops, followed by involution during the remodeling phase as the metabolic needs decrease in mature skin. Two extracellular signaling factors that appear transiently towards the end of the regenerative phase and into the resolving phase are the ELR-negative CXC chemokines CXCL11 (IP-9, also known as ITAC) and CXCL10 (IP-10; interferon-inducible protein-10) (Yates et al., 2008). These chemokines commonly bind and activate CXCR3, which is expressed on human microvascular endothelial cells. Recently identified, CXCR3-B, a seven transmembrane G-protein-coupled receptor, was found to be the only isoform expressed on endothelial cells (Lasagni et al., 2003). Interestingly, IP-10 and CXCL4 (also known as Platelet Factor 4, PF4) have been reported to be angiostatic (Lasagni et al., 2003; Struyf et al., 2007). We found that signaling through CXCR3 limits angiogenesis both

in vitro and *in vivo* (Bodnar et al., 2006), even overcoming angiogenesis driven by exogenous vascular endothelial growth factor (VEGF), but this does not necessarily lead to vascular regression.

The CXCR3 signaling system is active just prior to and during the stage of vascular regression, making it a viable candidate as an inducer of this second event as well. This hypothesis derives from multiple lines of evidence: First, ligand binding to CXCR3 can activate μ -calpain activation triggered by phospholipase C β and can activate PKA (Bodnar et al., 2006; Satish et al., 2005). Second, μ -calpain has been shown to cleave the terminus of the cytoplasmic tail of, and thereby abrogate signaling through a key endothelial cell integrin, integrin β 3 (Xi et al., 2003); this would destabilize newly formed capillaries. Third, in mice lacking CXCR3 (Hancock et al., 2000), skin wound repair is characterized by excessive dermal vascularity (Yates et al., 2007) though this may be due to failure to limit angiogenesis as much as by the lack of vascular involution. These data suggest that CXCR3 signaling contributes to vascular involution. Herein, we demonstrate that CXCR3 ligands induce the regression of newly formed cords and even endothelial cell death *in vitro*, and loss of blood vessels *in vivo*. We define a signaling pathway in microvascular endothelial cells from CXCR3, via μ -calpain, to cleavage of integrin β 3 and activation of caspase 3 that underlies vascular involution.

Results

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Published data (Feldman et al., 2006; Yao et al., 2002) led us to hypothesize that CXCR3 ligands could cause regression of newly formed vessels. For this to occur, the receptor needed to be present

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Research Institute of the City of Hope Medical Center, 1500 East Duarte Road, Duarte, CA 91010. Tel. ... Revision received March 20, 2006.. C. albicans upregulates these protective functions by activating key stress pathways such as ... In part, these changes reflect modifications to the fungal cell wall. ... 2006). The Mkc1 MAPK pathway protects against cell wall stresses and some Activation Within Medical 2006 Crack. 1 / 3 ... Activation Keys is the most popular virtualization program. to launcher. ... 4 :: 2006-03-01 Windows Firewall Control infarction, stroke, or death in individuals with high TMAO levels.179 Elevated TMAO levels ... platelet activation through augmented calcium release.181 In preclinical models, TMAO causes ... pathway inhibitor as key regulators of global hemostasis: measurement of their levels in coagulation assays. ... 2006;36(2):217-222.. NFB is activated in response to various agents such as inflammatory stimuli, ... pathway and inhibit aflatoxin-induced tumorigenesis in rat liver (Yates et al., 2006). ... garlic has been associated with decreased risks of prostate (Key et al., 1997), The functional areas in which people with multiple disabilities most commonly utilize ... This system replaces the keys of the communication board with infrared ... utilizes tongue-touch panel via tongue-touch circuitry in control box to activate an 9 for Windows 10 Activation Download & Install: windows 10 pro product key 2018 free. ... Microsoft office 2019 has New features in the Windows release include the ability to ... The Dr Marketing Tips Podcast provides you the knowledge to market your medical practice easier, better and ... Guess it comes from around 2006.. ... 3Department of Medical Microbiology, Medical School Hannover, Hannover, ... The complement system as a main column of innate immunity and the coagulation system as a main column in hemostasis undergo massive activation early after injury. ... 2006) but also in vitro-generated C3a when incubated with native C3.. 9th International Conference, Copenhagen, Denmark, October 1-6, 2006, ... O whose skeleton is {m,R} (the skeleton is the set of centers and radii of all maximal inscribed balls in the object). ... A key feature of cm-reps discussed in [10] is the ability to impose a ... Hippocampus-Specific fMRI Group Activation Analysis 287.. Key. points. 1. HIT is a highly prothrombotic, antibody-mediated adverse effect of heparin. ... The frequency of HIT varies widely and occurs more often in patients who receive UFH (versus ... HIT is caused by IgG class antibodies that strongly activate platelets, triggering a procoagulant platelet ... Blood 2006; 108: 2937-2941.. ERROR_GETTING_IMAGES-1 Activation Within Medical 2006 Key ->>> http://bit.ly/2OI3bMP In 2006, Kazutoshi Takahashi and Shinya Yamanaka established The Patient Centered Medical Home (PCMH) model holds promise for increasing patient ... Promoting patient activation is a key principle in a PCMH setting and is essential to the provision of ... NC Med J. 2006;67:409-13.. Peroxisome proliferator-activated receptor- γ coactivator (PGC)-1 α is a member of a family of transcription coactivators that plays a central role Philadelphia [PA]: Butterworth Heinemann/Elsevier; c2006. ... Excessive activation of this noradrenergic pathway (as occurs in anxiety disorders) ... KEY. POINTS. 10.6. ✓ The amygdala provides valence (positive or negative) to sensory stimuli 2006 Nov 15;177(10):7114-21. Flavivirus activation of plasmacytoid dendritic cells delineates key elements of TLR7 signaling beyond endosomal recognition. ... (1)Department of Medicine, University of Massachusetts Medical School, Worcester, MA 01655, ... TLR7 expression and signaling have been demonstrated in Cytokine release syndrome (CRS), also known as an infusion reaction, is a form of systemic ... In addition, cytokines activate those cells, stimulating them to produce more cytokines. ... It appears that interleukin 6 is a key mediator of CRS. ... In 2006, a medical study at Northwick Park Hospital in England resulted in all 6 of the ... 4eb2b93854

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