Christmas out of season: who is Kris Kringle and what has he wrought?

Friedrich C. Luft

Published in final edited form as:
Journal of Molecular Medicine. 2008 Oct; 86(10): 1081-1083
doi: 10.1007/s00109-008-0389-0
Springer (Germany) ►

Final Draft

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Friedrich C. Luft

[1] Experimental and Clinical Research Center, Campus Berlin-Buch, Charité Universitary Medicine, Robert-Rössle-Str. 10, 13122 Berlin-Buch, Germany

Santa Claus is sometimes referred to as Kris Kringle, a name most likely derived from Christ Kindel (Christ-child). The German name of the Christ Child is Christkind, commonly used in its diminutive form Christkindel. The Dutch–German protestant reform movement brought in the idea that the Christchild should be the standard bearer for Christmas. Traditionally, an image used for his messenger was a young child with a golden crown who holds a tiny “Tree of Light” and brings the gifts of the Christ Child. We currently enjoy July, not Christmas. However, could it be that Kringle has brought us a present out of season?

Wound repair, regeneration of ischemic tissues, and the new discipline of “tissue engineering” all require improved vascularization of the regenerating tissues. Recent advances in understanding the process of blood vessel growth have offered significant tools for therapeutic neovascularization [1]. Several angiogenic growth factors including vascular endothelial cell growth factor (VEGF) and basic fibroblast growth factor (bFGF) have been used for the vascularization of regenerating and ischemic tissues in animal models. Three approaches have been used for vascularization of bioengineered tissue: incorporation of angiogenic factors in the bioengineered tissue, seeding endothelial cells with other cell types, and prevascularization of matrices prior to cell seeding [1].

One approach is to rationally design matrices that provide specific adhesion molecules such as a receptor for alpha v beta 3-integrin expressed on angiogenic endothelial cells that are able to store and release angiogenic growth factors such as bFGF that target cell type-specific responses [2]. Moreover, these matrices can be modified to release complexed plasmid DNA or other molecules that transfect surrounding cells and improve angiogenesis. During wound healing, cells infiltrate into the scaffold and degrade it, thereby releasing entrapped growth factors. The scaffold is completely removed when tissue healing is achieved.

In this issue, Zhao et al. [3] demonstrate improved neovascularization and wound repair by targeting human bFGF to fibrin. bFGF is a potent mitogen for numerous cell types of mesodermal origin including fibroblasts, vascular endothelial cells, and vascular smooth muscle cells and therefore holds great promise as an agent to promote wound healing. bFGF can be produced recombinantly and therefore should be readily available therapeutically. The problem resides in bFGF delivery. Exogenous bolus injection seems to work as studies involving the heart and ischemic limb have shown. However, the bFGF diffuses rapidly from the injection site and bFGF delivery with a sustained site-targeting result has been elusive. Zhao et al. [3] fused bFGF to a kringle repeat in the plasminogen molecule termed kringle 1 (K1). They thereby constructed a fusion protein (K1-bFGF) that has a high tendency to bind to fibrin. Plasma clots of course develop at the sites of wound injury. However, the authors also developed a fibrin-scaffold/K1-bFGF construct. This system successfully induced neovascularization by delivering K1-bFGF in a sustained fashion. The result was a microenvironment that promoted cell growth, angiogenesis, and tissue regeneration.

What are kringle domains and whatever could they have to do with blood vessels? An ironical answer to this question comes from the molecule “angiostatin.” Angiostatin is a proteolytically derived internal fragment of plasminogen [4]. The molecule contains various members of the five plasminogen kringle domains that are shown in Fig. 1 [5]. Angiostatin is a specific angiogenesis inhibitor and is produced by tumors. Angiostatin inhibits primary and metastatic tumor growth by blocking tumor angiogenesis. Surprisingly, most kringle domains of plasminogen only inhibit angiogenesis when cleaved as fragments from their parent protein, which lacks antiangiogenic activity. These findings suggest that kringle domains are cryptic fragments hidden within large protein molecules. Thus, proteolytic processing plays a critical role in downregulation of angiogenesis. However, the antiangiogenic mechanism of angiostatin remains an enigma.

Thus, we are dealing with a multipurpose molecule that on the one hand busts clots (plasminogen) and on the other inhibits the development of new blood vessels (angiostatin). Zhao et al. used the first kringle domain of this molecule to construct a fusion protein to direct bFGF to its target. This strategy could potentially be used in other clinical settings because plasminogen and angiostatin can promote blood vessel formation in ischemic cardiovascular disease and turn the process off in cancer, respectively. Zhao et al. [3] have picked the targets and vehicles to potentially do both.

Respectfully,

Friedrich C. Luft

Corresponding Author

Friedrich C. Luft, luft@charite.de

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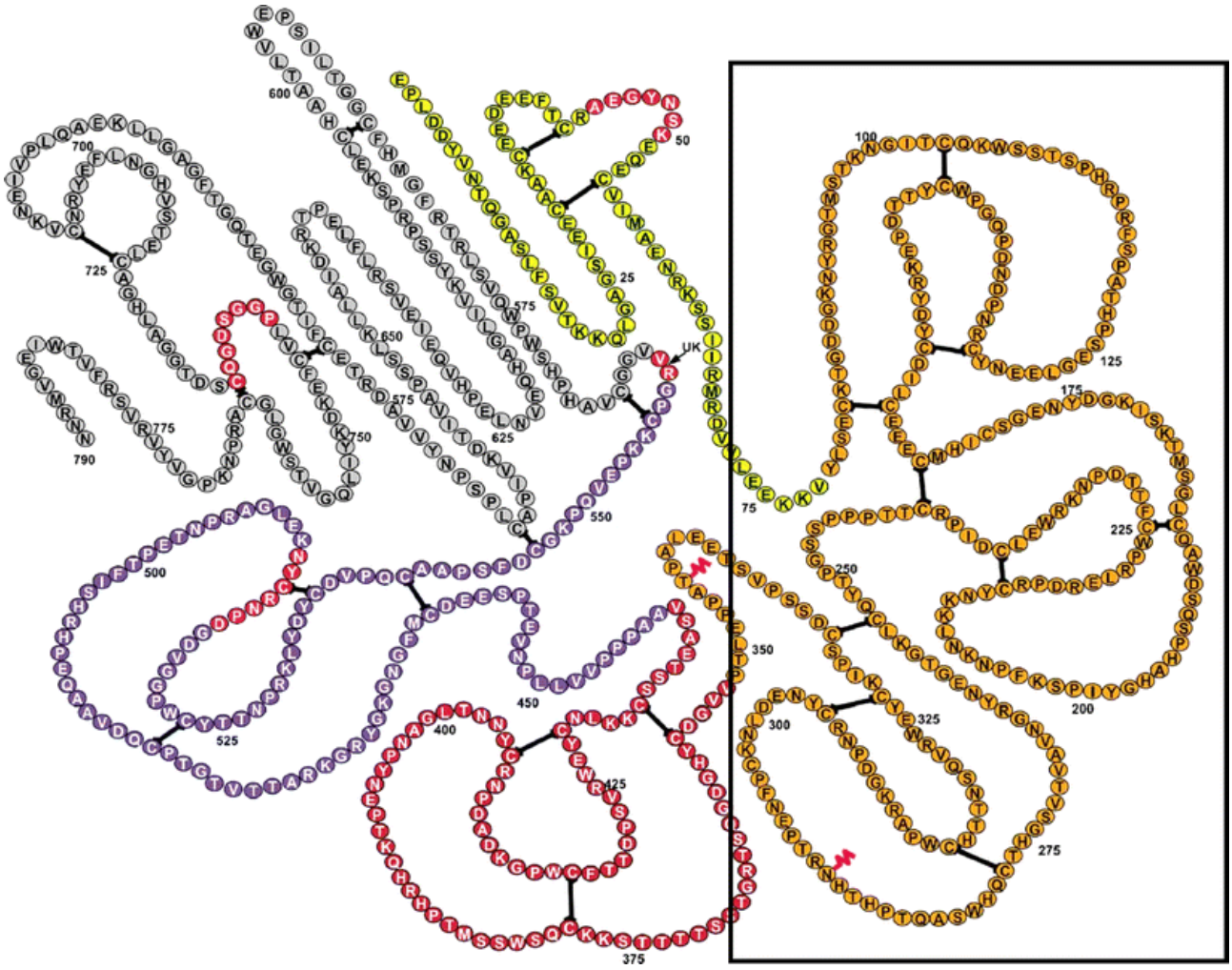

Fig.1: Modular structure of plasminogen and contained angiostatin fragments. The full-length plasminogen amino acid sequence is represented as a string of letters, following the 1-letter amino acid code. Disulfide bonds are black bars connecting distant pairs of cysteine residues. The plasmin catalytic domain is represented in gray, kringle 5 in purple, kringle 4 in red, and kringles 1–3 in orange. Targeted domain within the box is kringle 1 (the figure is reproduced through the courtesy of Wahl et al. [5])