Angiogenesis Inhibition

Introduction

The definition of Angiogenesis means formation of new blood vessels sprouting from existing ones (also referred to as neo-vascularization). This biological phenomenon only occurs in specific circumstances such as placental and foetal development, and wound healing. However, uncontrolled angiogenesis is also involved in many diseases such as tumour cancers (Van Hinsbergh et al., 1999; O’Reilly, 2003), arthritis (Bodolay et al. 2002), psoriasis (Xia et al. 2003), retinopathies (Takagi et al., 2003) etc... Therefore, the development of new, useful angiogenesis inhibiting compounds is one of the hot topics in new anti-cancer drug design. A lot of our current insight on neo-vascularization and tumour growth is attributed to the work of Dr. Folkmann (2002).

The complete angiogenesis process includes different steps. Endothelial cells which form the walls of the blood vessels have a great ability to divide and travel. The construction of a new vascular network requires following sequential steps:

1) Release of proteases from ‘activated’ endothelial cells
2) Degradation of the basement membrane surrounding the existing blood vessel
3) Migration of endothelial cells into the interstitial space
4) Endothelial cell proliferation
5) Tube formation and subsequent lumen formation
6) Generation of a new basement membrane with the recruitment of pericytes
7) Fusion of newly formed blood vessels
8) Initiation of blood flow

Discovery of angiogenesis inhibiting properties of jojoba flour

As explained in another part of this website (http://users.telenet.be/jojoba/doc/experiments/review.pdf) some of the observed biological activities during earlier feeding experiments could not be explained through pure food restriction solely. The severe growth retardation and non-development of the sexual organs in young animals was in great contrast to the temporary and reversible fertility drop in adult animals. The fact that adult mice receiving a threshold dose of refined, de-oiled jojoba flour did not suffer significant weight loss but were suppressed completely in their reproductive capacities during the whole treatment, led us to the discovery that angiogenesis inhibiting properties were present in jojoba flour. Interestingly, these properties have in the past been overlooked all of the time since they were mimicked by the severe food restriction using the flour in an overdose. In addition, in those early experiments unrefined jojoba meal was used which provoked supplementary problems due to the presence of anti-trypsin factors.

Experiments confirming angiogenesis inhibiting properties of certain specific jojoba flour components

Meanwhile, several experiments conducted at different laboratories and institutes have confirmed the presence of compounds with angiogenesis inhibiting properties in refined, de-oiled jojoba flour.

Certain Simmondsin derivates were able to:

1) Inhibit blood vessel development in fertilized chicken eggs
2) Inhibit VEGF-α and bFGF induced human endothelial cell proliferation
3) Inhibit VEGF induced in vitro tube formation of human endothelial cells in a 3-D fibrin matrix
4) Inhibit the ex-vivo outgrowth of tube-like structures from foetal mouse metacarpals
5) Inhibit in vivo neovascularization of matrigel chambers in mice
Discussion

The effect of dimethylsimmondsin on food restriction is a strong dose-depending phenomenon; this means that treatment doses must be fully respected. In our in vivo experiments in mice, a dose of 2.7% refined, de-oiled jojoba flour, containing approx. 0.27% bulk Simmondsins (approx. 0.14% dimethylsimmondsins, food intake inhibitors) and approx. 0.14% desmethyl- & didesmethylsimmondsins (angiogenesis inhibitors), were used. At this dose no significant weight loss was observed (because of the sub concentration of food intake inhibitors), but angiogenesis inhibiting properties were strong enough to suppress in vivo neovascularization in matrigel chambers and reproduction in mice. No other detrimental side effects on healthy cells, tissues or organs nor cytotoxic effects have been observed using the products at an appropriate dose. However, when higher doses of dimethylsimmondsin are used, severe side-effects can be observed upon long term administration. York et al. (2000) described that dimethylsimmondsins have profound effects on the hematopoietic system; however these experiments were conducted with 0.5% of dimethylsimmondsin in the diet (causing more than 50% weight loss), a dose which is more than 3 times the dose we recommend. It should be clear that each medicine or biological active compound has to be used at the appropriate dose; most medicines used at an exaggerated dose will provoke side-effects upon long usage. Yet, there is no argument to believe that Simmondsin derivates could not be used to constitute new angiogenesis inhibiting drugs to cure, for example, cancers, upon condition the appropriate dose is respected.

Conclusion

The use of certain specific jojoba compounds as food restricting agent, anti-conceptive but sure as angiogenesis inhibitor are worthwhile to investigate further. Topical formulations to cure diseases through skin administration like psoriasis and arthritis are currently under development. However, much more research is needed on the exact mechanism of angiogenesis inhibition for each Simmondsin derivate, its pharmacokinetic behaviors, dose-response curves etc... before safe oral or parenteral applications can be developed.

Reference list


