Inhibitory effect of lycopene on PDGF-BB-induced signalling and migration in human dermal fibroblasts: a possible target for cancer

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Abstract
Tumours are complex tissues composed of both matrix proteins and stromal cells such as fibroblasts and inflammatory cells. Tumour progression is often the result of dynamic interactions between the tumour cells and their surroundings. Lycopene, a natural carotenoid that is abundant in tomato, has been shown to inhibit proliferation of several types of cancer cells through arrest of tumour cell-cycle progression, IGF-1 (insulin-like growth factor 1) signalling transduction, induction of apoptosis etc. However, in our recent study, we found that lycopene inhibited PDGF-BB (platelet-derived growth factor-BB)-induced signalling and cell migration in human cultured skin fibroblasts through a novel mechanism of action, i.e. direct binding to PDGF-BB. Trapping of PDGF by lycopene also compromised melanoma-induced fibroblast migration and attenuated signalling transduction in fibroblasts simulated by melanoma-derived conditioned medium, suggesting that lycopene may interfere with tumour-stroma interactions. The trapping activity of lycopene on PDGF suggests that it may act as an inhibitor on stromal cells, tumour cells and their interactions, which may contribute to its anti-tumour activity.

Stromal cells are involved in key metastatic processes
Although cancers are initiated through genetic mutation, progression is often the result of dynamic interactions between the tumour cells and their surroundings. Tumours are not merely masses of neoplastic cells but, instead, are complex tissues composed of both a non-cellular (matrix proteins) and a cellular ‘diploid’ component (tumour-associated fibroblasts, capillary-associated cells and inflammatory cells) [1]. It is increasingly evident that these stromal cells are involved in key metastatic processes of tumour, including proliferation, matrix degradation, and migration [2]. For example, in melanoma development and progression, the interactions between melanoma cells and fibroblasts are through several pathways. Autocrine growth factors [bFGF (basic fibroblast growth factor), IL-8 (interleukin 8), HGF (human growth factor) and PDGF (platelet-derived growth factor)] stimulate proliferation and migration of the melanoma cell itself. Paracrine growth factors such as PDGF and other growth factors modulate the microenvironment, especially stromal fibroblasts, to the benefit of melanoma growth, invasion and metastasis [3].

PDGF is involved in angiogenesis and tumorigenesis
Abnormalities of PDGFR (PDGF receptor)/PDGF are thought to contribute to a number of human diseases, and especially malignancy. PDGF stimulates autocrine growth of tumour cells and regulates tumour stromal fibroblasts and tumour angiogenesis [4]. In cutaneous remodelling, studies ex vivo revealed that PDGF-BB is a mitogen and a mitogen for dermal fibroblast chemotaxis [5]. Other studies have also emphasized the significance of tumour-derived PDGF-A (and potentially PDGF-C) and PDGFR-α signalling in the recruitment of an angiogenic stroma that produces VEGF-A (vascular endothelial growth factor-A) and other angiogenic factors [6]. The roles of PDGF/PDGFR in cancer are detailed in a review [7]. Among them, chromosomal translocation resulting in excess PDGF-B leads to dermatofibrosarcoma protuberans. Overexpression of PDGFR and/or ligand is found in brain tumours and diverse malignancies.

Effect of lycopene on cancer cell proliferation
Lycopene, responsible for the characteristic deep red colour, represents more than 80% of total tomato carotenoids. This compound increases approx. 20-fold during fruit ripening [8]. A considerable body of epidemiological evidence demonstrates an association between tomato consumption and reduced prostate cancer risk. The Health Professionals Follow Up Study [9] showed that the estimated intake of
lycopene (in the form of tomato-based products), but not of other carotenoids, is linked to lower prostate cancer risk. Many studies also demonstrated that lycopene can inhibit proliferation of several types of cancer cells, including those of breast, lung and endometrium [10]. The mechanisms of action involved in the prevention of prostate cancer have been extensively studied, including arrest of cell-cycle progression, induction of apoptosis, up-regulation of connexin expression, reduction of prostate-specific antigen and IGF-1 (insulin-like growth factor 1) signalling transduction and overall decrease in prostate tumour aggressiveness [11,12].

**Trapping of PDGF by lycopene as a possible target for cancer prevention**

In our recent study, we found that lycopene inhibited human PDGF-BB-induced signalling in human cultured fibroblasts, including human Hs68 and primary cultured skin fibroblasts (H.S. Chiang, W.B. Wu, J.Y. Fang, D.F. Chen, B.H. Chen, C.C. Huang, Y.T. Chen and C.F. Hung, unpublished work). PDGF-BB-induced phosphorylation of PDGFRβ, ERK1/2 (extracellular-signal-regulated kinase 1/2), p38 and JNK (c-Jun N-terminal kinase) was attenuated by lycopene in a concentration-dependent manner. Lycopene at 0.5 μM was sufficient to exert its inhibitory effect on PDGF-induced signalling in human fibroblasts. In line with this, skin fibroblast migration on gelatin and collagen was also inhibited by pre-incubation of PDGF-BB with lycopene. Surprisingly, a further analysis using the dot binding assay revealed that lycopene directly bound to human PDGF-BB in PBS and human plasma, indicating that lycopene can interact with PDGF-BB under in vitro and in vivo conditions. This is consistent with the observations by our laboratory that lycopene but not β-carotene also directly interacts with rat PDGF-BB and inhibits PDGF-BB-induced proliferation and migration in rat smooth-muscle cells [13]. Sequence alignment has shown that mature rat and human PDGF-B chain share 93% similarities in their primary sequence, suggesting that lycopene may interact with their homologous region(s). In our functional studies, we found that trapping of PDGF-BB by lycopene subsequently inhibited melanoma-induced fibroblast migration in a non-contact-modified Boyden chamber co-culture system and attenuated signalling transduction in fibroblasts simulated by melanoma-derived conditioned medium, indicating that lycopene affects tumour–stroma cell interactions. Therefore the trapping activity of lycopene on PDGF may contribute to the inhibition of signalling in stromal fibroblasts and then their interactions, which suggests the possible effect of lycopene on melanoma progression.

**Concluding remarks**

As an antioxidant, many studies have been focused on the correlation between lycopene’s antioxidant activity and anticarcinogenesis. However, the findings presented here and recent findings by others and us suggest that lycopene and tea catechins, the flavonoid polyphenols with the antioxidant activity, possess anti-tumour activity through a novel mechanism of action other than their antioxidant activity [14,15]. There have been several exciting success stories in the clinical targeting of tumour stroma [16]. The inhibition of PDGF binding to its receptor by lycopene may represent a general principle in modulation of growth factor signalling, which may decrease tumour progression.

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**References**


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