REGIONAL CENTRE FOR BIOTECHNOLOGY

Journal Club

"Angiotensin inhibition enhances drug delivery and potentiates chemotherapy by decompressing tumour blood vessels"

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Seminar room

Abstract

Cancer and stromal cells actively exert physical forces (solid stress) to compress tumour blood vessels, thus reducing vascular perfusion. Tumour interstitial matrix also contributes to solid stress, with hyaluronan implicated as the primary matrix molecule responsible for vessel compression because of its swelling behaviour. Here we show, unexpectedly, that hyaluronan compresses vessels only in collagen-rich tumours, suggesting that collagen and hyaluronan together are critical targets for decompressing tumour vessels. We demonstrate that the angiotensin inhibitor losartan reduces stromal collagen and hyaluronan production, associated with decreased expression of proýbrotic signals TGF-b1, CCN2 and ET-1, downstream of angiotensin-II-receptor-1 inhibition. Consequently, losartan reduces solid stress in tumours resulting in increased vascular perfusion. Through this physical mechanism, losartan improves drug and oxygen delivery to tumours, thereby potentiating chemotherapy and reducing hypoxia in breast and pancreatic cancer models. Thus, angiotensin inhibitors-inexpensive drugs with decades of safe use could be rapidly repurposed as cancer therapeutics.