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Luteolin, ellagic acid and punical acid are natural products that inhibit prostate cancer metastasis

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Prostate cancer is the second cause of cancer deaths in men in the United States. When the cancer recurs, early stages can be controlled with hormone ablation therapy to delay the rate of cancer progression but, over time, the cancer overcomes its hormone dependence, becomes highly aggressive and metastasizes. Clinical trials have shown that pomegranate juice (PJ) inhibits prostate cancer progression. We have previously shown that the PJ components luteolin (L), ellagic acid (E) and punical acid (P) together inhibit growth of hormone-dependent and -independent prostate cancer cells and inhibit their migration and chemotaxis towards CXCL12, a chemokine that is important in prostate cancer metastasis. Based on these findings, we hypothesized that L+E+P inhibit prostate cancer metastasis *in vivo*. To test this possibility, we used a Severely Combined Immuno-Deficiency (SCID) mouse model in which luciferase-expressing human prostate cancer cells were injected subcutaneously near the prostate. Tumor progression was monitored with Bioluminescence Imaging weekly. We found that L+E+P inhibits PC-3M-luc primary tumor growth, inhibits the CXCL12/CXCR4 axis for metastasis and none of the tumors metastasized. In addition, L+E+P significantly inhibits growth and metastasis of highly invasive *Pten*^{-/-}; *K-ras*^{G12D} prostate tumors. Furthermore, L+E+P inhibits angiogenesis *in vivo*, prevents human endothelial cell (EC) tube formation in culture and disrupts pre-formed EC tubes, indicating inhibition of EC adhesion to each other. L+E+P also inhibits the angiogenic factors IL-8 and VEGF as well as their induced signaling pathways in ECs. *In conclusion*, these results show that L+E+P inhibits prostate cancer progression and metastasis.

Biography

Manuela Martins-Green is Professor of Cell Biology at the University of California Riverside. She holds a doctorate in Developmental Biology (1987) and continued her education at the Lawrence Berkeley National Laboratory with Dr Mina Bissell (1988-1991) supported by a three-year National Research Service Award from the National Cancer Institute. She then was an Adjunct Assistant Professor at Rockefeller University in the laboratory of Dr. H Hanafusa before taking joining the University of California Riverside in 1993. She leads a successful research laboratory that focuses on the biology of Wound Healing and on Prostate Cancer. One group in the Martins-Green laboratory works on understanding how wounds become chronic so that treatments can be developed for this very serious societal problem. The other group works on identifying components of pomegranate juice that inhibit prostate cancer metastasis and in understanding the mechanisms involved in such inhibition. The components of the juice affect basic cellular mechanisms involved in metastasis which has led the group to speculate that these components will be effective in inhibiting the metastasis of other cancers.

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