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Optimization of anti-angiogenesis therapy using mathematical tools

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Abstract: Intensive research in the last two decades has increased the understanding of the angiogenesis process, and has established its significance in clinical cancer. However, since cause and effect relationships in this complex system are as yet to be clarified, the clinical research into new anti-angiogenic therapies still suffers from the lack of predictive tools (1). In order to examine the potential effects of novel anti-angiogenic therapies and their exact schedules we have developed a detailed algorithm for the dynamical analysis of tumor growth, the process of angiogenesis, and the process of vascular maturation. The algorithm describes the interactions between the multiple molecular, cellular and multi-cellular elements, which together influence tumor growth dynamics. The algorithm also takes into account the different temporal parameters, which characterize reaction rates in the angiogenesis process. Implementing the algorithm in a computer model one can analyze the versatile effects of drugs on the growth and decay of both the tumor, and the immature and mature blood vessels, as well as on the induction of an array of relevant growth factors, including Angiopoietin-1, Angiopoietin- 2, Vascular Endothelial Growth Factor and Platelet-Derived Growth Factor. Our analysis shows that Angiopoietin-1 has a significant dichotomic effect: Medium levels are stimulatory, whereas both low and high levels are inhibitory for tumor growth. Note that a similar effect was demonstrated for VEGF. Our theoretical simulations are supported by surprising experimental results, showing that both inhibition and over-production of Angiopoietin-1 suppress tumor growth (2). Our results, in conjunction with the aforementioned experiments, pinpoint the significance of mathematical tools for designing and optimizing anti-angiogenic therapy. 1. Jain R.K., 2001, Nat.Med 7:987-9. 2. Hayes A.J., 2000 Br.J.Cancer 83:1154-60. 3. Shim W.S.N., 2001 Int.J.Cancer 94:6-15.