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Institution för Mikrobiologi, Tumör och Cell biologi

Mechanistic Study of Antiangiogenic Agents in Cancer Therapy

AKADEMISK AVHANDLING

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ABSTRACT

Tumor growth and metastasis are dependent on angiogenesis that constantly alters the tumor microenvironment. Based on the antiangiogenic principle proposed more than 40 years ago by Dr. Judah Folkman, antiangiogenic drugs (ADs) are successfully developed and are routinely used in combination with chemotherapeutics for treatment of various cancers in human patients. However, nearly 10-year clinical experiences with these drugs have taught us some unexpected outcomes that are mechanistically challenging. These include: 1) Ineffective antiangiogenic monotherapy; 2) Modest therapeutic benefits in combination with chemotherapy; 3) Development of intrinsic and evasive drug resistance; 4) Broad adverse effects; 5) Timeline of treatment; 6) Searching for reliable and predictive biomarkers for patient selection and monitoring therapeutic efficacy. Currently, mechanisms underlying these important clinical issues remain poorly understood. In this thesis, we aimed to study the mechanisms that underlie clinical benefits of ADs, clinical adverse effects related to antiangiogenic therapy and interplay between different factors in the tumor microenvironment in modulation of tumor growth and drug responses. In the first published paper, we show that tumor-derived VEGF enters the circulation and causes a systemic effect by alteration of vessels numbers and structures in various tissues and organs. This systemic effect, which we term as cancer-associated systemic syndrome (CASS), is similar to paraneoplastic syndrome, often seen in cancer patients, manifesting anemia, endocrine dysfunction, and hepato-splenomegaly. Based on these findings, we hypothesized that treatment of high VEGF-expressing tumors with chemotherapeutics that often have hematopoietic suppressive effect would cause severe defects of bone marrow hematopoiesis. Indeed, treatment of high VEGF-expressing tumor-bearing mice results in severe anemia, leading to early demise of animals. Prior to chemotherapy, delivery of antiangiogenic agents markedly prevents chemotherapy-induced hematopoietic suppression. From this study we conclude: 1) Sequential delivery of ADs followed by chemotherapeutics is a preferred regimen; and 2) Reduction of chemotoxicity by ADs is, at least in part, a mechanism that underlies combination therapy. In the second paper, we show that PlGF, a member of the VEGF family, negatively regulates VEGF-induced tumor angiogenesis and tumor growth by the formation of PlGF-VEGF heterodimers. Notably, PlGF-overexpressing mouse and human tumors demonstrate superior sensitivity to ADs. Thus, PlGF may potentially be used as a surrogate marker to predict antiangiogenic therapy. In the third paper, we demonstrated that systemic delivery of ADs to mice causes a broad systemic effect on healthy vasculatures in various tissues and organs. These “off-tumor” effects in general correlated well with clinical adverse effects of these drugs in cancer patients. Thus these findings provide a new mechanistic insight of antiangiogenic therapy-related side effects. In the fourth paper, we show a new protocol of studying lymphangiogenesis, which is essential for lymphatic metastasis.