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One in Place, Another One to Go

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Editorial

Two papers in this special issue review were selected for publication because of their timely topic. The paper by French and Frazier [1] brings us up to date on the state of the art of our knowledge of basic and applied science for vascular endothelial growth (VEGF). Because VEGF has been considered a specific angiogenic agent, the inhibition of its activity either using antagonists of its signaling pathway or monoclonal antibodies directed against its receptor was thought to be the cornerstone of newly developing specific antitumor strategy. This notion was buttressed by recent findings about integral roles of VEGF singaling in vascular integrity, modulation of extracellular matrix, hypoxic responses, tumor immunoreactivity and stem cell recruitment. All these and many other issues are well covered by French and Frazier The importance of VEGF in tumor biology has been confirmed by studies on overexpression of VEGF in several tumor types and its correlation with poor prognosis [2] and on responsiveness of tumors to anti-VEGF therapy. VEGF-A levels (in particular the $VEGF_{206}$ isoform) have been demostrated to be increased in mammary, lung, brain, pancreatic, ovarian, kidney, and bladder carcinomas. Moreover, studies on transgenic animals indicate that VEGF acts not only as an angiogenic growth factor but also as an autocrine agent directly stimulating the proliferation of primary tumor cells and the growth of metastatic lesions [3,4].

French and Frazier also emphasize the importance of VEGF-C and VEGFR-3 in lymphangiogenesis, and thus in cancer progression. Newly developed anti-VEGF-C or anti-VEGFR-3 agents are capable of blocking lymphangiogenesis, and thus cancer progression at least in rodent models [5,6]. If successful in human clinical trials this would represents a truly novel approach to chemotherapy.

Avastin® (bevacizumab), manufactured by Genentech, represents one of the first examples of commercially successful biologicals. This compound is a monoclonal anti-VEGF antibody that has been used in combination with classic chemotherapeutic drugs to treat patients with metastatic carcinoma of the colon or rectum, patients with unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer, and patients who have not received chemotherapy for metastatic HER2-negative breast cancer [7]. Though it was withdrawn recently by the FDA from the line of approved drugs for treatment of advanced breast cancer, a couple of recent studies have shown effectiveness of Avastin in treatment of early breast cancer [8,9]. The addition of bevacizumab to neoadjuvant chemotherapy led to a statistically significant increase in remission rate of HER2-negative breast cancer though this was accompanied by increased rate of side effects, seen in patients treated with anti VEGF agents, such hypertension, left ventricular dysfunction and certain infections in both studies [8,9].

The second paper in this issue raises the awareness of readers for granulins, a less known family of growth factors [10]. Though the first progranulin or PGRN, the so called transforming growth factor e, was first described as a mitogen primarily for epithelial cells back in 1987 [11], the recognition of its significance is only a recent phenomenon. In addition to its mitogenic activity for both epithelial and mesenchymal, it also participates in embryonic development; wound healing, CNS function among others. Though the therapeutic potential is largely unexplored, the overexpression of granulins in several cancers (of breast, ovary, prostate, brain, hepatocellular carcinoma) but not in others (lung, endometrial carcinoma) raises the possibility of proliferation promoting effect of granulins in specific tumors. The assumed role progranulin plays in carcinogenesis is at least partially due to its mitogenicity, therefore potential therapeutic benefit would have to be connected with inhibition of receptor activation or signal transduction. However, relatively little is known about granulin receptor and signal transduction systems, especially in the upstream pathways. That might be a reason why the scientific community lags behind in developing biological therapeutic agents based on granulins. What we know indicates that PGRN binds with sortilin on cell surfaces which is likely to be part of a protein turnover mechanism [12]. PGRN also binds to and inhibits the TNF-receptors, and associates with the Toll-like receptor-9 [10]. These interactions are important in the regulation of inflammation.

The likely unusual signaling pathway suggests that targeting mediators in this pathway might lead to fewer side effects than experienced with other inhibitors directed towards targets within signaling pathways of VEGF, PDGF and EGF where there is a lot of similarities, and therefore crosstalk among molecules, thus resulting in sometimes unexpected side effects. However, new studies show that downstream in the PRGN pathway there is convergence with other signaling pathways, such as activation of the MAPK and PI3K signaling systems, though the details vary with different cell types and tumors. Interestingly, unlike some other growth factors PRGN possesses the ability to initiate mitosis on its own (e.g., in fibroblasts lacking the IGF-1 receptor) [10]. Whether that means that targeting of upstream molecules will be more specific or whether it will lead to modification of downstream mediators is difficult to predict. Perhaps more feasible approach would the disruption of PRGN binding to components of the extracellular matrix, such as perlecan or integrin. Going in a different direction, Park et al. devised a strategy using RNA interference targeting the GRN gene to suppress proliferation of cancerous cells *in vitro* and also to suppress growth of tumors after transplantation of such into Balb/C nude mice [13].

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It is also possible that disturbances of progranulin signaling pathway play more essential and, perhaps more importantly, specific role in the pathogenesis of certain degenerative CNS diseases than in carcinogenesis. For example, a mutation in a copy of the human GRN gene results in a form of frontotemporal lobar dementia that is characterized by neuronal atrophy in the frontal and temporal cerebral lobes and that usually afflicted middle aged people. Bigni et al. entertain the possibility that specific pharmacological agents can counteract progranulin haploinsufficiency in patients with this type of dementia carrying GRN mutation [14].

Granulin is a growth factor we should pay close attention to in the near future.

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