MOLECULAR PATHWAYS FOR LYMPHANGIOGENESIS
AND THEIR ROLE IN HUMAN DISEASE

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The dysfunction or proliferation of lymphatic vessels (lymphangiogenesis) is linked to a number of pathological conditions including lymphedema and cancer (Baldwin et al., 2002; Stacker et al., 2002). The recent discovery and characterisation of the lymphangiogenic growth factors vascular endothelial growth factor-C (VEGF-C) and VEGF-D and of their receptor on lymphatic endothelial cells, VEGFR-3, has provided an understanding of the molecular mechanisms controlling the growth of lymphatic vessels (for review see Stacker et al., 2004a). In addition, other genes and protein markers have been identified with specificity for lymphatic endothelium that have enhanced the characterization and isolation of lymphatic endothelial cells.

In cancer there is evidence that expression of the lymphangiogenic factors VEGF-C and VEGF-D can induce the formation of tumor lymphatic vessels which are associated with spread of the primary tumor to local lymph nodes (Mandriota et al., 2001; Skobe et al., 2001; Stacker et al., 2001). Human tumor xenografts engineered to express these factors have increased lymphatic vessels and a greater capacity to produce lymphogenous metastasis. In these studies the use of monoclonal antibodies and other inhibitors to the factors can prevent these effects (He et al., 2002; Stacker et al., 2001). These studies using animal models are supported by the correlation found between the expression of these factors in primary human tumors and clinical parameters relating to tumor metastasis, in particular lymph node spread (Stacker et al., 2002; Stacker et al., 2004b). Hence, it may be beneficial to inhibit these molecules in cancer to restrict metastatic spread (Achen et al., 2005).

Conversely, the use of lymphangiogenic growth factors to induce the formation of new lymphatic vessels provides a potential method to treat conditions such as lymphedema where lymphatic vessel function is inadequate (Baldwin et al., 2002). The pro-lymphangiogenic effects could also be of benefit in areas such as tissue repair. The proof-of-principle for using lymphangiogenic growth factors to grow lymphatic vessels in healthy tissue and tissue affected by lymphedema has been described in the literature (Rutanen et al., 2004; Szuba et al., 2002).

Our growing understanding of the molecules that control lymphangiogenesis allows us to design more specific drugs with which to manipulate the relevant signalling pathways (Achen et al., 2005; Stacker et al., 2004a). Modulating these pathways and other molecules with specificity to the lymphatic system could offer alternative treatments for a number of important clinical conditions.
REFERENCES


