Chapter 3

INTERLEUKIN-8 AND ANGIOGENESIS

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Abstract: Interleukin-8 (IL-8) is an angiogenic CXC chemokine produced by a variety of cell types. Although initially described as a chemokine for neutrophils, IL-8 has become known as a potent angiogenic factor, involved in normal physiological processes such as wound healing, and abnormal processes such as cancer metastasis. IL-8 is secreted by numerous solid tumour types and associated inflammatory cells, and has been shown to exert a potent angiogenic effect via paracrine and autocrine routes in tumourigenesis, and as such represents an valid opportunity for intervention in cancer metastasis.

1. ANGIOGENESIS AND METASTASIS

Angiogenesis is the complex process of the generation of new blood vessels from pre-existing vessels. In normal physiological events, angiogenesis plays a vital part, including embryonic development, wound healing and endometrial proliferation (1). During such processes, angiogenesis is highly regulated and is only turned on for brief periods, before complete inhibition (2). Angiogenesis can however, occur under abnormal, pathological conditions such as arthritis, retinopathy and cancer metastasis. Under these conditions, the angiogenic process is persistent and unregulated.

Growth and development of a tumour requires transport of nutrients to and removal of waste products from the tumour site (1). Local diffusion will suffice for tumours up to 2mm in diameter, but for tumours to continue to grow, a connection must be made to the blood supply. The process of creating such a stable blood source is mediated by many angiogenic factors (Figure. 1). Tumours must then continually stimulate the growth of new capillary blood vessels for continued growth. The blood vessels within the tumour can then provide a route for detached tumour cells to enter the circulatory system and metastasize to distant sites (2, 3). The capillary vessels formed are composed of endothelial cells and pericytes. For angiogenesis to occur, endothelial cells must be stimulated by angiogenic factors.
The tumour cells themselves do not have to be the only source of angiogenic signals: associated inflammatory cells, such as macrophages may be recruited and activated to produce angiogenic activity (1,2).

There are many different growth factors, chemokines and cytokines that have been shown to exert an angiogenic effect, including basic fibroblast growth factor (bFGF), hepatocyte growth factor/scatter factor (HGF/SF), vascular endothelial growth factor (VEGF), PDGF, TNF-α, IL-1 and IL-8. Growth at the tumour site (both primary and secondary loci) requires that angiogenesis be initialised. Activation is achieved by a change in the balance of inhibitory and stimulatory factors in favour of stimulation (4).

Increased levels of angiogenic factors can induce tumour angiogenesis, with decreased levels of angiogenic inhibitors by cancer cells, vascular endothelial cells & other stromal cells(5). As most tumour cells are surrounded by stroma, interaction between the stroma and the malignant cells are extremely important in the development of tumour angiogenesis (5).

2. INTERLEUKIN-8: A CXC CHEMOKINE

2.1 CXC Chemokines

Chemokines are cytokines that were originally identified as exhibiting chemotactic activity toward specific types of leukocytes. They are low molecular weight proteins - 8 to 12 kDa- with a basic nature and an affinity for heparin (6). Chemokines have molecular identity in the conservation of four cysteine residues which are essential for their tertiary structure, with disulfide bridges forming between either cysteines 1 and 3, or between cysteines 2 and 4 at the NH₂ terminus (7, 8). The family members include CXC, CC, C and CX3C chemokines, of which CXC and CC are by far the largest and well-defined groups (6, 9). In CXC chemokines the first two cysteines are separated by a non-conserved amino acid residue (the CXC cysteine motif) and mainly interact with neutrophils (8, 10). These cytokines in their monomer forms are around 10 kDa and appear to have pro-inflammatory and reparative activities (10). CXC chemokines are produced as precursor molecules containing a signal sequence of between 17 and 34 amino acids, which after cleavage produce a mature protein of 70 to 103 amino acids (8). CXC chemokines can be divided into two categories, depending whether or not they have the Glu-Leu-Arg (ELR) motif in front of the first cysteine residue (7, 8). Those that have the Glu-Leu-Arg (ELR) motif are predominantly angiogenic; those without are generally angiostatic (8, 10, 11, 12), Table 1, suggesting that CXC chemokines may function in regulating neovascularisation (13). They are non-glycosylated and the genes for all CXC chemokines (except for one, SDF-1) are located on chromosome 4q 12-21 (8, 14). CXC chemokines have between 20 and 50% homology at the amino acid level. Chemokines can be produced by many different cell types after stimulation with endogenous and/or exogenous inducers (8).

As mentioned previously, the balance between angiogenic and angiostatic factors at a tumour site is critical in regulating the angiogenic status of the local milieu. There has been increasing evidence to suggest that CXC ELR+ chemokines and their receptors play an important role in upsetting the normal balance in solid tumours (11).