Chemokine Receptors in Melanoma: CCR9 Has a Potential Role in Metastasis to the Small Bowel

As with most cancers, the primary lesions of melanoma do not kill patients. Rather, the metastases that appear in the brain, liver, lung, and other sites are the leading causes of morbidity and mortality in patients. Whereas clinicians have long known that certain cancers tend to metastasize to certain organs, the molecular factors that regulate organ-selective metastasis are poorly understood.

Seminal work by Zlotnik and colleagues (Müller et al., 2001) suggested that specific chemokine receptors (Rossi and Zlotnik, 2000), families of related G-protein-coupled, seven-transmembrane spanning cell surface receptors, and their ligands (chemokines) could be involved in organ-selective tumor metastasis. Müller et al., as well as our own group (Murakami et al., 2002), demonstrated that a limited number of chemokine receptors are expressed by cancer cell lines and that CXCR4 facilitates lung and lymph node metastasis of breast cancer and melanoma cells. Other reports suggested that expression of CCR7 (Wiley et al., 2001; Mashino et al., 2002) by various forms of cancer may enhance lymph node metastasis and that CCR10 may facilitate tumor progression in the skin (Murakami et al., 2003). In all these cases, the chemokine ligand that binds to each of the three receptors above is expressed at high levels in the specific tissues where metastases frequently occur.

Melanoma also metastasizes frequently to the gastrointestinal tract. Indeed, up to 60% of patients show evidence of gastrointestinal metastases at autopsy (Blecker et al., 1999). Nearly 50% of these metastases are in the small bowel, but others appear in the colon or anorectum. In this issue of the JID, Letsch et al. (2004) examine the role of CCR9 in melanoma metastases to the small bowel. They explored this possibility because the CCR9 ligand, CCL25 (TECK), was previously shown to be selectively and constitutively expressed in the epithelium of the small bowel and thymus (Wurbel et al., 2000), and thus represents a potential “attractive force” for melanoma cells that express CCR9. Letsch et al. found that eight of 20 melanoma cell lines showed functional CCR9 expression. Interestingly, three of the CCR9-positive cell lines were derived from resections of small bowel metastases, and one line (established from a nodal metastasis) was obtained from a patient who eventually developed a small bowel metastasis. Letsch et al. also demonstrated that metastatic melanoma cells isolated immediately following resection of a small bowel metastasis showed CCR9 expression, suggesting that the expression of CCR9 was present in vivo at the site of metastasis.

Why do melanoma cells and other cancer cells express chemokine receptors? Whereas chemokine receptors have traditionally been recognized for their ability to stimulate directional migration (or “chemotaxis”) of cells, other functions of these receptors may be critical in their ability to regulate organ-selective metastasis. Recent evidence suggests that CCR10 may enable melanoma cells to elude immune attack by activation of the prosurvival kinase Akt (Murakami et al., 2003). Other receptors, including CXCR4, may increase the ability of cancer cells to arrest on blood vessels that express CXCL12 (SDF-1) (Cardones et al., 2003), to alter migratory properties (Robledo et al., 2001), or to enhance survival (Murakami et al., 2002).

The roles of CCR9/CCL25 (TECK) in small bowel metastasis may be analogous to those of CCR10/CCL27 in progression of melanoma in the skin, perhaps promoting retention of these cells in the environs of the small bowel through prosurvival pathways. Of note, both CCL25 and CCL27 show nearly exclusive expression in the skin and gut, respectively. Moreover, skin-homing and gut-homing populations of T cells express high levels of CCR10 and CCR9, respectively, enabling them to home more effectively to these important sites of immune surveillance (Homey et al., 2002; Onai et al., 2002).

Plausible roles for chemokine receptors in organ-selective metastasis are emerging. Specific production or localization of chemokines in various tissues increases the potential for tumor cells bearing the appropriate receptor to localize and, perhaps more importantly, to survive at these sites. In several of the animal models described in the reports above, blockade of chemokines or their receptors led to impressive inhibition of experimental metastasis, suggesting that antagonism of chemokine receptor pathways in cancer patients may be a novel and rational therapy for reducing the devastating effects of metastasis in patients with melanoma and other cancers.

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References

Blecker D, Abraham S, Furth EE, Kochman ML; Melanoma in the gastrointestinal tract. Am J Gastroenterol 94:3427–3433, 1999

Abbreviations: CCL, chemokineligand; CCR, chemokine receptor; CXCR, CXC chemokine receptor; TECK, thymus-expressed chemokine

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