Minireview

Targeting sphingosine-1-phosphate for cancer therapy

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This review summarises some important new findings that implicate sphingosine-1-phosphate (S1P) as a potent tumorigenic and angiogenic agent released from cancerous tumours into the tumour microenvironment. Also explored is the novel concept that bioactive lipid signalling molecules, like S1P, can themselves be targets for rational drug design, thereby opening up an entire class of lipidomic-based therapeutics for oncology and other human diseases.

Keywords: tumour microenvironment; bioactive lipid signaling; sphingosine-1-phosphate; lipidomics; angiogenesis

SPHINGOSINE-1-PHOSPHATE, A BIOACTIVE LIPID WITH TUMORIGENIC EFFECTS

Until recently, phospholipids and their derivatives were considered 'neutral' in that they were thought either to serve a simple structural role in cell membrane organisation or to provide energy for beta oxidation, glycolysis and other metabolic processes. It has only recently been appreciated that many lipids have significant roles as bioactive signalling mediators. Good examples of such bioactive lipids include: (i) the eicosanoids (such as the cannabinoids and the leucotrienes), (ii) phospholipids and their derivatives such as phosphatidic acid and platelet activating factor, (iii) lyso phospholipids such as lysophosphatidyl choline and lysophosphatidic acid (LPA) and (iv) certain sphingolipids.

Sphingolipid signalling mediators represent a group of extracellular and intracelllar signalling molecules with pleiotropic effects on important cellular processes, including cancer (Ogretmen and Hannun, 2004). Figure 1 shows the key elements of the sphingolipid signalling cascade, including the bioactive-lipid mediators, ceramide (CER), ceramide-1-phosphate (C1P), sphingosine (SPH) and sphingosine-1-phosphate (S1P). These mediators are derived from sphingomyelin, which is present in the plasma membranes of all mammalian cells.

Although much attention has been paid to S1P as a pleiotropic mediator required for normal embryonic development, particularly for cardiogenesis, vasculogenesis and angiogenesis (Liu et al., 2000), S1P has only recently been appreciated for its roles in lymphocyte trafficking, inflammation, cardiovascular and neurological disorders and tumour biology (Hla, 2004; Gardell et al., 2006). The major source of S1P is that produced from SPH through the action of sphingosine kinase (SPHK) (Taha et al., 2006). The pleiotropic biological activities of S1P are mediated via a family of G protein-coupled receptors (GPCRs) originally known as endothelial differentiation genes (EDG). Five GPCRs have been identified as high-affinity S1P receptors (S1PRs): S1P1/EDG-1, S1P2/EDG-5, S1P3/EDG-3, S1P4/EDG-6 and S1P5/EDG-8 only identified as late as 1998 (Lee et al., 1998). Many responses evoked by S1P are coupled to different heterotrimeric G proteins (Gα, Gβ, Gγ) and the small GTPases of the Rho family (Gardell et al., 2006).

In the adult, S1P is released from platelets (Murata et al., 2000) and mast cells to create a local pulse of free S1P (sufficient enough to exceed the Kd of the S1PRs) for promoting wound healing and participating in the inflammatory response. Under normal conditions, the total S1P in the plasma is quite high (300–500 nM); however, it has been hypothesised that most of the S1P may be ‘buffered’ by serum proteins, particularly lipoproteins (e.g., HDL > LDL > VLDL) and albumin, so that the bio-available S1P (or the free fraction of S1P) is not sufficient to appreciably activate S1PRs (Murata et al., 2000). If this were not the case, inappropriate angiogenesis and inflammation would result.

As early as the 1860s, Rudolf Virchow proposed that cancerous tumours occur at sites of chronic inflammation. In 1986, H F Dvorak speculated that tumours are ‘wounds that do not heal’ (Dvorak, 1986). One could argue that the ability of cancer cells to release S1P into the tumour microenvironment is consistent with the idea that cancerous tumours release mediators to trick the body into thinking that it has a wound that needs the infiltration of platelets, fibroblasts, mast cells and neutrophils for the purpose of creating an inflammatory response. The infiltrating cells promote further release of S1P into the tumour microenvironment with the resulting manifestation of the tumorigenic and proangiogenic effects of S1P (Figure 2).

SPHINGOSINE-1-PHOSPHATE IS TUMORIGENIC

It has been suggested that the balance between CER/SPH levels vs S1P provides a rheostat mechanism that decides whether a cell is sent into the death pathway (via CER and/or SPH) or is protected from apoptosis by S1P. One of the key regulatory enzymes of the sphingolipid rheostat mechanism is SPHK, whose role is to convert the death-promoting sphingolipids, CER and SPH, into the growth-promoting S1P. In most, but not all of the cell types...
tested, S1P promotes cell proliferation and is involved in
chemotaxis and cytoskeletal rearrangement via the Rho signalling
system.

Cancer cells are notorious for being opportunistic in co-opting
key signalling systems. As such, they take advantage of the
sphingolipid rheostat by promoting conditions that favour the
SPHINGOSINE-1-PHOSPHATE AND TUMOUR ANGIogenesis

Angiogenesis is the process by which new blood vessels are formed from existing vasculature. The angiogenesis process associated with tumours (tumour angiogenesis) is considered to be a crucial component of disease progression. Antiangiogenic therapeutics is particularly attractive because vascular endothelial cells (ECs) do not mutate as easily as do cancer cells; consequently, ECs are less likely than cancer cells to gain resistance to prolonged therapy, making them good potential targets for therapeutics. The antiangiogenic approach to cancer has been greatly advanced by the recent FDA approval of the antiangiogenic drug, bevacizumab (Avastin\textsuperscript{TM}, Genentech, South San Francisco, CA, USA) to treat colon cancer as an adjunct to cytotoxic chemotherapy.

A growing body of recent evidence implicating S1P as one of the most potent proangiogenic agents comes from studies directly comparing S1P with agents such as VEGF and bFGF. Sphingosine-1-phosphate stimulates DNA synthesis and chemotactic motility of human venous ECs (HUVECs), whereas inducing differentiation of multicellular structures, all of which is suggestive of S1P’s role in early blood-vessel formation (Lee et al., 1999; Liu et al., 2000; Argraves et al., 2004). Also, S1P promotes the migration of bone marrow-derived EC precursors to neovascularisation sites (Annabi et al., 2003). Cells that overexpress S1P\textsubscript{1} are resistant to the antiangiogenic agents thalidomide and Neovastat (Annabi et al., 2003). In addition, it has been demonstrated that substantial cross-talk exists between S1P and other proangiogenic growth factors such as VEGF, EGF, PDGF, bFGF and IL-8. For example, S1P transactivates EGF (Shida et al., 2004) and VEGF\textsubscript{2} receptors (Spiegel and Milstien, 2003) and VEGF upregulates S1P\textsubscript{1} receptor expression (Igarashi et al., 2003). Also, S1P, acting via S1P\textsubscript{1} and the ‘VEGF axis,’ is required for hind-limb angiogenesis and neovascularisation (Chae et al., 2004).

The most direct in vivo evidence that S1P contributes to tumour angiogenesis comes from our recent publication that focused on a murine monoclonal antibody (mAb) designed to neutralise extracellular S1P by molecular absorption (Visentin et al., 2006). In various \textit{in vitro} assays using HUVECs, the anti-S1P mAb neutralised tube formation, migration of vascular ECs and protection from cell death, each of which is S1P-induced. Sphingosine-1-phosphate increased new capillary growth into Matrigel plugs implanted in mice, an effect that was neutralised by the systemic administration of the anti-S1P mAb. The mAb substantially neutralised bFGF- and VEGF-induced angiogenesis in a murine Matrigel plug assay, and the antibody mitigated S1P stimulated the release of proangiogenic cytokines (VEGF, IL-8 and IL-6) from tumour cells \textit{in vitro} and \textit{in vivo}. Importantly, mice xenografted with orthotopically placed human cancer cells exhibited substantial retardation of tumour progression with anti-S1P mAb treatment. This was demonstrated in murine models of human breast, ovarian and lung cancer and in one allograft model of murine melanoma (Visentin et al., 2006).

TARGETING S1P AS A LIPIDOMIC-BASED THERAPEUTIC INTERVENTION

It is now well accepted to target the protein ligand of a receptor (e.g., Avastin targets VEGF; Remicade and Humira target TNF\textalpha) for the purpose of intervening in the signalling cascade that would otherwise have been activated by the ligand–receptor interaction. Monoclonal antibodies like Avastin have been particularly useful as molecular sponges to selectively absorb and neutralise the protein ligands that would otherwise activate receptors. The anti-S1P mAb is potentially valuable in that it is a reagent that targets a bioactive-lipid ligand, in this case S1P. By comparison with large protein ligands like VEGF (35 000–44 000 Da), the lipid target, S1P, is a small molecule (379 Da) and, as a consequence, has only one epitope (i.e., the polar head group) to target for antibody recognition (inset of Figure 1). Unlike the successful work with anti-PGE2 mAbs (Portanova et al., 1996), academics and industry researchers have not been successful in developing mAbs that inhibit bioactive lysolipids like S1P and LPA with antibody specificity, affinity and other performance characteristics suitable for preclinical proof-of-concept work. This leads one to argue that sphingomab may be a drug of an emerging discipline that may be termed lipidomic-based therapeutics.

A few notable exceptions (e.g., folic acid targeted by methotrexate), the vast majority of the > 500 molecular drug targets are proteins. Second to protein targets are nucleic acids, accounting for about 2% of the total targets. The focus on proteins was a natural consequence of our evolving understanding of biochemistry, which allowed researchers to identify potential protein targets involved in key metabolic and signalling pathways. Some of the first drugs developed by the rational drug design approach to the scientific method came after the discovery of key enzymes, receptors and ion channels as they emerged in the basic science literature. One can argue that target identification now is driven by the technological developments of proteomics and genomics, both of which reflect our persistent ‘protein-centric’ view of drug discovery.

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Now, the field of lipidomics (a subset of ‘metabolomics’) has emerged (Wenk, 2005) and provides new opportunities for drug discovery. As was the case for proteomics and genomics, tools of measurement led the way. For lipidomics, the development of electrospray tandem mass spectrometry and other tools has facilitated our understanding of the cellular lipidome, and we now believe that there are over 1000 members of the lipidome, opening up an entire array of new potential targets for therapeutic interventions.

It has been recognised that alterations in lipid metabolism can lead to cancer, cardiovascular disease, diabetes, neurodegenerative disorders, immune function, pain, mental disorders and inflammation. However, only as a consequence of our recent appreciation that bioactive lipids are bona fide signalling molecules have key members of the functional lipidome been viewed as targets for rational drug design. The best example of signalling lipids to target might be prostaglandins as proinflammatory agents. The Cox-2 inhibitors designed to mitigate prostaglandin production not only are effective NSAIDs but are now proving useful in clinical trials for cancer therapy.

Of late, the attractiveness of the sphingolipid group of bioactive lipids as targets has been fuelled by the recent discovery, beginning largely in the mid-1990s, that many small-molecule lipid mediators are ligands for GPCRs (e.g., SIP and LPA on EDG receptors), ion channels (e.g., SPC action on ScAMPER) and/or modulators of key kinases (e.g., PH action on PKC) and transcription factors (e.g., LPA action on PPAR). When searching for functional lipidome for new anticancer targets, researchers with a protein-centric view focus on the lipid proteome, rather than on the lipidome itself. As such, in the antishpingolipid-therapeutics arena, several pharmaceutical and biotechnology companies have chosen the classical approach of targeting enzymes of the sphingolipid biosynthetic pathway, such as SPHK1, or one or more of the five GPCRs identified for SIP (SIP1–5).

Unfortunately, targeting SPHK is somewhat complicated by the finding that SPHK1 and SPHK2 may have opposite actions (Maceyka et al., 2005a). Sphingosine kinase is thought to be translocated to the surface membrane and to produce/release the extracellular SIP that is tumorigenic and proangiogenic. Thus, SPHK1 is thought to produce the extracellular SIP that protects cancer cells from proapoptotic cytotoxics (Figure 2). On the other hand, SPHK2 induces apoptosis and inhibits growth (Maceyka et al., 2005b). The SPHK2 is likely to produce SIP exclusively for intracellular signalling.

Because of the divergent roles of the two SPHK isoforms, a SPHK-targeted anticancer therapeutic would have to selectively inhibit SPHK1 and not SPHK2. This may prove to be difficult, as both enzymes have five highly conserved domains and the resulting high-percent identity in their amino-acid sequences. In addition, several splice variants of both isoforms have been characterised and a third isoform of SPHK has been recently identified (Bektas et al., 2005b), thus further complicating target selectivity. Novagen’s anticancer genestein derivative, phenoxydiol, currently in Phase 3 trials, is thought to have some activity as an inhibitor of SPHK (Gamble et al., 2006).

Other SPHK-independent sources of SIP have been suggested. One such player is the exoenzyme, autotaxin, which is capable of producing SIP from SPC (Clair et al., 2003). Potential additional sources of SIP like the autotaxin story may explain why sphk1-null mice exhibited no significant changes in tissue SIP levels even though tissue SPHK activity was nearly eliminated (Allende et al., 2004). However, autotaxin KO mice exhibited no significant changes in SIP levels either (van Meeteren et al., 2006); so, it remains unclear as to how dominant SPHK is as the sole source of tissue or blood SIP.

Another classical approach to intervening in the sphingolipid pathway is preventing SIP from interacting with its compliment of S1PRs. The potential success of this strategy has been simulated by studies showing that the antineoplastic and antiangiogenic effect of the sphingolipid analogue, FTY720 (Lamontagne et al., 2006) can be attributed to its downregulation of four of the five S1PRs (Cuvillier and Levade, 2003). One complication to the antireceptor approach is that not all S1PRs mediate tumorigenic responses. Although SIP1, and SIP3, are responsible for the proproliferative, promigratory and antiapoptotic effects of SIP, SIP2 has been shown to have the opposite effects on cell migration and other responses (Goparaju et al., 2005; Sanchez et al., 2005). Thus, as is the case with SPHKs, targeting S1PRs may be complicated by the presence of multiple isoforms with opposing actions on tumour cells, and selectivity of receptor antagonism will be a key element in successful sphingolipid receptor-based therapeutic interventions.

A more direct approach that avoids these limitations is the prevention of ligand binding to all cognate receptors, the approach that could be used by the highly specific mAb to SIP. Preclinical data demonstrate that this approach deprives growing tumour cells of important growth and survival factors and largely mitigates tumour angiogenesis (Visentin et al., 2006). Because of the important role of sphingolipids in cancer progression, it has been argued that sphingolipid-based therapeutics will be the next generation of cancer treatments (Milstein and Spiegel, 2006).

CONCLUSION

The use of the anti-SIP mAb as a research tool has provided strong evidence that SIP has several mechanisms of action in promoting cancer, including: (i) direct effects of SIP on tumour-cell growth and metastatic potential, (ii) direct angiogenic effects on ECs in their tumour angiogenesis roles and (iii) indirect angiogenic effects of SIP in stimulating the release and action of other proangiogenic growth factors such as VEGF (Figure 2). This work, as well as recent strides in our understanding of the cellular lipidome, gives credence to an emerging area of drug discovery called lipidomic-based therapeutics that directly targets pleiotropic bioactive lipids involved in cancer as well as other disorders.

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