Met decoys: Will cancer take the bait?

Inappropriate Met receptor tyrosine kinase signaling can produce proliferative, invasive, angiogenic, and antiapoptotic activities that contribute to malignant growth. Met can be activated by paracrine or autocrine mechanisms in a ligand-dependent fashion, or be constitutively activated by mutation and by other ligand-independent mechanisms. Because Met is inappropriately expressed in almost all types of human cancer, the HGF/SF-Met signaling pathway should be an exceptional target for cancer intervention strategies and therapies. In this issue of *Cancer Cell*, two reports show that the extracellular domain of Met is an important target for developing anticancer therapies.

The receptor tyrosine kinase (RTK) Met is the receptor for hepatocyte growth factor/scatter factor (HGF/SF). Aberrant signaling driven by inappropriate activation of Met is one of the most frequent alterations observed in human cancers and plays a crucial role in tumorigenesis and metastasis (Birchmeier et al., 2003; Trusolino and Comoglio, 2002). Inappropriate Met activation can arise by ligand-dependent and -independent mechanisms, which include overexpression of Met and/or HGF/SF, paracrine or autocrine activation, or constitutive activation through gain-in-function mutations. Activated Met recruits signaling effectors to its multidocking site located in the cytoplasmic domain (Figure 1), resulting in the activation of several key signaling pathways, including Ras-MAPK, PI3K, Src, and Stat3. These pathways are essential for tumor cell proliferation, invasion, and angiogenesis, and for evading apoptosis. Targeting the HGF/SF-Met pathway is becoming an attractive approach for developing therapeutic drugs that potentially would have activity against a wide range of human cancers (http://www.vai.org/vari/metandcancer/index.aspx) by inhibiting processes essential for malignant growth.

In the past few years, many different strategies have been developed to attenuate aberrant Met signaling in various human cancer cells. These strategies target, directly or indirectly, the Met receptor and/or its ligand HGF/SF. As depicted in Figure 1, direct methods include: (1) neutralizing antibodies against HGF/SF or the use of the HGF/SF antagonist NK4 to prevent ligand access to Met (Cao et al., 2001; Date et al., 1998), (2) dominant/negative Met molecules or small molecule ATP binding site inhibitors to Met that block kinase activity (Furge et al., 2001; Christensen et al., 2003), (3) engineered SH2 domain polypeptides that interfere with access to the multidocking site (Atabey et al., 2001), and (4) RNAi or ribozymes that reduce receptor or ligand expression (N.S., unpublished data; Abounader et al., 2002). Most of these approaches display selective inhibition of Met signaling. Indirect inhibition of Met signaling can be achieved by blocking Met downstream signaling pathways, such as the MAPK, PI3K, or Stat3 pathways, which contribute to the malignant features of Met (Birchmeier et al., 2003). Small molecules such as geldanamycin have also been shown to inhibit Met (Webb et al., 2000).

In this issue of *Cancer Cell*, two groups report that targeting the extracellular domain of Met may be a promising new approach for human cancer intervention. Kong-Beltran et al. (2004)

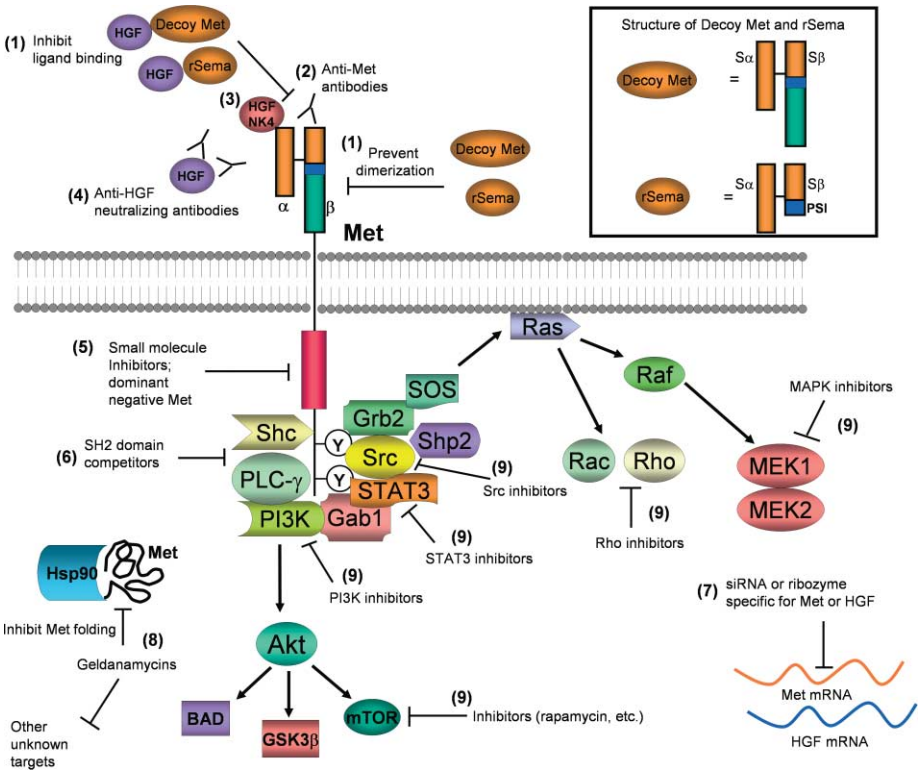

Figure 1. Met receptor tyrosine kinase: Sites and strategies for therapeutic intervention

Potential therapeutic strategies are: (1) decoy Met receptor (decoy Met) or recombinant Met Sema domain (rSema) inhibit ligand (HGF/SF) binding and presumably Met dimerization as well (decoy Met consists of the entire extracellular region and rSema consists of the Sema and PSI domains [see right upper box]), (2) anti-Met antibodies inhibit Met receptor dimerization and/or ligand binding, (3) HGF NK4 competes for HGF binding of Met, (4) anti-HGF neutralizing antibodies bind HGF and prevent Met stimulation, (5) small molecule inhibitors or dominant negative Met target the kinase domain and inhibit Met phosphorylation/activation, (6) SH2 domain competitors occupy the multidocking site and inhibit signal transduction, (7) siRNA or ribozyme specific for Met or HGF mRNA, (8) geldanamycin and derivatives suppress Met activity presumably through binding to Hsp90 and inhibiting molecular chaperone function, and (9) potential small molecule inhibitors or dominant negative forms of downstream signaling molecule of Met.

demonstrate that Met can dimerize in an HGF/SF-independent manner, and that both receptor dimerization and ligand binding requires the Sema domain. These authors also provide evidence that both recombinant Sema domain and an anti-Met Fab recognizing the Sema domain can inhibit Met activation in vitro. By a similar approach, Michieli et al. (2004) have engineered a soluble Met consisting of the entire extracellular region, called decoy Met, that is delivered in a lentivirus vector. Decoy Met inhibits tumor growth and spontaneous metastases of human xenografts in immunocompromised mice. The most interesting aspect of this decoy is its ability to inhibit HGF/SF-dependent as well as HGF/SF-independent Met activation. These data suggest that targeting the extracellular region of Met can be an alternative therapeutic strategy for treating human cancers by simultaneously blocking the ligand binding as well as presumably preventing receptor dimerization.

It is noteworthy that decoy Met also shows an inhibitory effect on Met-negative tumor xenograft growth by impairing host Met-dependent angiogenesis. However, this effect is transient, and tumor cells eventually catch up to the untreated tumors, suggesting that selection of an alternative signaling pathway(s) may occur to enable tumor cells to grow under less vascular environments. Therefore, the use of decoy Met should only be considered in combination with inhibitors to the alternative signaling pathway.

The Sema domain is required for HGF/SF binding and Met dimerization, but it is still not clear how it interferes with the ligand receptor complex formation. As with most targeted inhibitors, toxicity related to expression of Met in normal tissues may also be an issue. Met is a member of a subfamily of receptor tyrosine kinases which includes Ron and Sea, and the Sema domain is conserved in all semaphorins and plexins (Trusolino and Comoglio, 2002). This homology with the receptor may lead to pleiotrophic interactions. Therefore, additional in vivo studies are required to address potential toxicity. It is encouraging that toxicity studies in mice by Michieli et al. showed no adverse effects with long-term exposure to decoy Met. However, the decoy was human, not mouse Met, and specificity might be a factor in reducing toxicity. Another issue is whether a lentiviral vector is optimal, considering that the viral vector can persist indefinitely and viral integration would be undesirable. In this regard, the recombinant Sema domain or the Met Fab-recognizing Sema domain would be a better choice for therapy, yet in vivo activity needs to be tested.

In the future, a complete image of HGF/SF-Met complex by crystallization of active HGF/SF with full-length Met receptor will provide an even stronger structural basis for designing new therapies. High-resolution crystallographic images will allow us to understand what residues are required for the dimerization and ligand binding in the Sema domain, how the "activated" multidocking sites recruit downstream molecules, and how the ATP binding site in the kinase domain mediates the intermolecular tyrosine phosphorylation. Peptidomimetic inhibitors or other small molecules specifically targeting Met can be designed based on the crystallographic knowledge, and this could become a trend for future therapeutic approaches. In such a way, small molecule drugs that are easy to synthesize, easy to modify, easy to deliver, and probably at low cost, would be advantageous.

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Selected reading

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