Sp1king out cancer (....and fibrosis?)

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Abstract It is becoming increasingly apparent that many of the basic mechanisms underlying cancers also underlie fibrotic diseases. For example, the Sp1 family of transcription factors plays an essential role in controlling the gene expression of proteins that promote both oncogenesis and fibrogenesis. The drug mithramycin, which prevents Sp1 binding to DNA, has been in use clinically for some cancers, but has side-effects. However, other drugs exist that affect Sp1 activity through promoting Sp1 protein degradation. Evidence has emerged that low levels of mithramycin can be combined with these drugs to result in potent antitumorigenic effects without resulting in obvious toxicity (Gao et al. *Cancer Res* 2011 Jun 20; Jia et al. *Cancer Res* 70:1111–1119, 2010). Given that Sp1 proteins also promote expression of profibrotic genes such as collagen type I and CCN2, it is possible that this combinatorial approach may be taken in the future to block not only cancer but also fibrosis.

Keywords ccn2 · Collagen · Connective tissue growth factor · Pancreatic cancer · Mithramycin · Cancer · Sp1 · Betulinic acid · Tolfenamic acid

The Sp1 family of transcription factors is over-expressed in a variety of cancers and plays an important role in regulating the expression of vascular endothelial growth factor (VEGF) and angiogenesis (Finkenzeller et al. 1997; Shi et al. 2001; Black et al. 2001). Mithramycin, a natural molecule that was first identified in the soil bacterium

Streptomyces argillaceus, reversibly binds to double stranded DNA in GC-rich regions and hence interferes with the DNA binding, and hence activity of, the Sp1 family of transcription factors (Ray et al. 1989; Blume et al. 1991). Mithramycin has been used to treatment a variety of cancers including tumor-associated hypercalcaemia, testicular tumors and myeloid leukemia (Queisser et al. 1988; Schaiff et al. 1989; Archimbaud et al. 1989). Unfortunately, mithramycin has toxic side-effects including hepatotoxicity (26%), nausea/vomiting (23%), and serum creatinine level elevation (5%) (Zojer et al. 1999); thus, recently, mithramycin has fallen out of favor clinically.

However, other drugs, betulinic acid and tolfenamic acid, targeting Sp1 exist. Rather than blocking the binding of Sp1 to DNA, these drugs act by a different mechanism of action than mithramycin. Specifically, these drugs promote the proteasome-dependent degradation of the Sp1 family of transcription factors. Betulinic acid, a pentacyclic triterpene natural product, induces antiangiogenic and proapoptotic responses in both LNCaP cells and in tumors due to activation of selective proteasome-dependent degradation of the Sp1 family of transcription factors (Chintharlapalli et al. 2007). Tolfenamic acid, a nonsteroidal anti-inflammatory drug that is a potent inhibitor of prostaglandin biosynthesis and used to treat migranes, also facilitates Sp1 protein degradation (Abdelrahim et al. 2006). Crucially, recent evidence has revealed that low doses of mithramycin can be combined with either betulinic acid or tolfenamic acid resulting in beneficial antitumorigenic effects in pancreatic cancer without obvious toxic side-effects (Jia et al. 2010; Gao et al. 2011).

In addition to playing a role in cancers, a role for the Sp1 family of transcription factors in fibrosis, in particular for promoting the expression of profibrotic proteins such as type I collagen and CCN2 (connective tissue growth factor)

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in fibroblasts (Li et al. 1995; Vindevoghel et al. 1997; Hitraya et al. 1998; Sandorfi et al. 2005; Holmes et al. 2003; Fajardo et al. 2011; Kum et al. 2007; Park et al. 2009), has long been appreciated. Collectively, these data suggest that a combinatorial approach of attacking Sp1 binding to DNA and protein stability might be beneficial in combating not only cancer, but also fibrotic disease.

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