ABSTRACT

sFRP4 is a member of secreted frizzled related protein family of Wnt- inhibitors that binds directly to Wnt and antagonize both canonical and non-canonical Wnt pathway (Kawano and Kypta 2003). Down regulation of sFRP4 has been implicated in various types of malignancies including prostate and cervix cancer (White et al 2009; Constantinou et al 2008; Drake et al 2003; Hsieh et al 2003). Other members of the sFRP family have been shown to modulate vascular cell proliferation in-vitro and in-vivo (Ezan et al 2004). Recent report by Goodwin et al. has shown that sFRP4 and sFRP2 are not expressed in most of the endothelial cells (Goodwin et al 2006). Growing body of evidences show that Wnt plays an important role in the development of vasculature under different conditions that include embryonic angiogenesis as well (Masckauchán and Kitajewski 2005). We hypothesized that administration of sFRP4 will modulate the endothelial cell physiology and angiogenesis there of.

The present study investigates the role of sFRP4 on the endothelial cell physiology using in-vitro models and effect on physiological and tumor angiogenesis using in-vitro and in-vivo models. The results of the present study show that administration of sFRP4 inhibits angiogenesis in cell culture and in vivo. sFRP4 administration inhibits endothelial cell migration, we also found a decrease in tube formation property of endothelial cells upon sFRP4 treatment. The study shows that sFRP4 was able to block neovascularisation
in chick embryo vascular bed. Our findings were further confirmed by different in-vivo angiogenesis assays.

We have further dissected the mechanism of action of sFRP4 in endothelial cells. Our study shows that sFRP4 administration increases the levels of superoxide radicals and hydrogen peroxide release from endothelial cells, thereby indicating that sFRP4 administration imparts redox stress to endothelial cells. Further, we show that long term administration of sFRP4 induces endothelial cell apoptosis.

In summary our work focuses on the novel role of sFPR4, as an inhibitor of angiogenesis. sFRP4 inhibits the formation of blood vessels in vitro and in-vivo. sFRP4 has been implicated in different types of cancer and different other anomalies, but this study for the first time shows a direct effect of sFRP4 on endothelial cells and its anti-angiogenic potential. Various anti-angiogenic drugs are being used as combination therapy for treatment of solid state tumors. There is growing evidence that anti-angiogenic drugs do improve future therapies of diseases like cancer, rheumatoid arthritis and ocular neovascularisation (Hagedorn et al 2000). A lot of research is being carried out to discover new drug molecules for anti-angiogenesis therapies. Our finding has brought into light a novel candidate for regulation of angiogenesis. sFRP4 is a very promising candidate to be used for therapeutic purposes for treatment of various types of cancers and other diseases like rheumatoid arthritis, ENL (Erythema nodosum leprosum) and ocular neovascularisation. Future works in the direction will see sFRP4 as an important molecule for anti-angiogenic therapy.