

## GETTING TO THE HEART OF THE MATTER: CCN2 PLAYS A ROLE IN CARDIOMYOCYTE HYPERTROPHY

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### ABSTRACT

**Connective tissue growth factor (CTGF/CCN2) is overexpressed in diabetes. Diabetic rats possess myocardial and cardiomyocyte hypertrophy. In a recent report, Wang and colleagues (Am J Physiol Cell Physiol. 2009 Jul 22. [Epub ahead of print]) show that CCN2 directly mediates cardiomyocyte hypertrophy as well as that induced by high glucose and fatty acid. CCN2 acted via the TrkA receptor. These data are the subject of this commentary, and emphasize that CCN2 may be an excellent target for therapy in diabetes.**

Diabetes not only characterized by kidney failure but also can cause acute and chronic heart failure (diabetic cardiomyopathy) characterized by cardiac hypertrophy, apoptosis and excess accumulation of extracellular matrix (Karnick et al., 2007; Feuvray and Darmellah, 2008). The proadhesive matricellular protein CCN2 is overexpressed in diabetes and can promote hypertrophy, apoptosis and fibrosis (Leask and Abraham, 2006). Although CCN2 has been proposed as a target for drug therapy in diabetes (Mason, 2009), whether CCN2 contributes to diabetic cardiomyopathy is unknown.

A recent report by Wang and colleagues (2009) showed that recombinant CCN2 could directly promote both apoptosis and hypertrophy in a cardiac myocyte cell line. Glucose and the fatty acid palmitate induced both apoptosis and hypertrophy in the same cell line. Glucose and the fatty acid palmitate induced CCN2 mRNA and protein, and siRNA against CCN2 significantly reduced the apoptosis and hypertrophy caused by these agents. Previously, it had been shown that CCN2 can bind and activate the TrkA receptor in human kidney mesangial cells (Wahab et al., 2005). Wang and colleagues (2009) found that pharmacological inhibition of TrkA blocked aspects of CCN2 activity.

That fatty acids can induce CCN2 lengthens the list of agents, which were initially believed to include only TGF $\beta$ , to promote CCN2 mRNA and protein expression (Blom et al., 2002). These data are significant as these strongly suggest that anti-CCN2 strategies may be useful in targeting several aspects of diabetes in addition to diabetic nephropathy and retinopathy (Mason, 2009), and also suggest that CCN2 may contribute to additional pathologies induced by fatty acids including fatty liver disease (Paradis et al., 2001). Future efforts, no doubt, will be focused on expanding the scope of these studies to animal models and, ultimately, humans.

## REFERENCES

Blom IE, Goldschmeding R, Leask A. Gene regulation of connective tissue growth factor: new targets for antifibrotic therapy? *Matrix Biol.* 2002 Oct;21(6):473-82.

Feuvray D, Darmellah A. Diabetes-related metabolic perturbations in cardiac myocyte. *Diabetes Metab.* 2008 Feb;34 Suppl 1:S3-9.

Karnik AA, Fields AV, Shannon RP. Diabetic cardiomyopathy. *Curr Hypertens Rep.* 2007 Dec;9(6):467-73.

Leask A, Abraham DJ. All in the CCN family: essential matricellular signaling modulators emerge from the bunker. *J Cell Sci.* 2006 Dec 1;119(Pt 23):4803-10

Mason RM. Connective tissue growth factor(CCN2), a pathogenic factor in diabetic nephropathy. What does it do? How does it do it? *J Cell Commun Signal.* 2009 Feb 14.

Paradis V, Perlemuter G, Bonvoust F, Dargere D, Parfait B, Vidaud M, Conti M, Huet S, Ba N, Buffet C, Bedossa P. High glucose and hyperinsulinemia stimulate connective tissue growth factor expression: a potential mechanism involved in progression to fibrosis in nonalcoholic steatohepatitis. *Hepatology.* 2001 Oct;34(4 Pt 1):738-44

Wahab NA, Weston BS, Mason RM. Connective tissue growth factor CCN2 interacts with and activates the tyrosine kinase receptor TrkA. *J Am Soc Nephrol.* 2005 Feb;16(2):340-51.

Wang XY, McLennan SV, Allen T, Tsoutsman T, Semsarian C, Twigg SM. Adverse effects of high glucose and free fatty acid on cardiomyocytes are mediated by connective tissue growth factor. *Am J Physiol Cell Physiol.* 2009 Jul 22. [Epubahead of print]