3. Background and objectives

3.1. Background

Clinically, AKI is considered a calamitous condition with incidences allied with high morbidity and mortality (Hoste et al., 2018; Silver et al., 2018). Among several risk factors for AKI, DM remains the major one (Takiyama & Haneda, 2014; Yu & Bonventre, 2018). Epigenetic mechanisms like HPTMs are key contributors to inflammatory diseases including diabetes and AKI (Reddy & Natarajan, 2015); yet, they have received relatively lesser attention as compared with the involvement of primary DNA sequence variations. Among HPTMs, histone methylation, and the regulatory enzymes; HMTs i.e., SET7/9 impart the pivotal role in kidney diseases via regulating inflammatory and apoptotic gene expression (Reddy & Natarajan, 2015). ***However, the role of HMT-SET7/9 in the regulation of inflammatory and apoptotic genes in the development of AKI under diabetic and non-diabetic conditions is highly elusive*** ***(Figure 3.1)*****.**

Evidence has strongly supported the prominent role of AT1R and ACE in the progression of the pathogenesis of AKI (Macconi et al., 2009; Ono et al., 2015). Despite the treatment with ARBs, and ACEi, morbidity, and mortality of these diseases remain high; hence there is an intense need for new therapeutic strategies (Alabdan et al., 2016; Bellomo et al., 2012; Kocak et al., 2016). The pressor arm of RAS is well explored but studies on depressor arm are still quite limited. Kidney diseases like diabetic nephropathy, the AT2R and ACE2 exerted the reno-protective effect by decreasing hypertrophy, causing vasodilatation, modulating inflammatory (NF-κB) and apoptotic (MAPK, PARP) pathways (Bonventre & Yang, 2011; Oudit et al., 2010; Park et al., 2009; Siragy, 2007). ***However, the role of AT2R and ACE2 in regulating the oxidative stress, inflammation, apoptotic signaling under diabetes-AKI comorbidity has yet not been explored.*** Despite noteworthy advances in dialysis techniques that assure the management of AKI in hemodynamically unstable patients with shock, AKI is still associated with multiple organ failure (heart, brain, liver) and inadmissibly high mortality rate (Lee et al., 2018). Hence, focusing only on kidney injury and loss of renal function possibly not be sufficient to improve outcomes of AKI patients. Existing data from basic and clinical research have begun to explain complex organ interactions in AKI settings between the kidney and other organs, including the brain,

heart and liver. Still, ***the exact underlying molecular mechanisms triggering distant organ dysfunction remain less understood.***

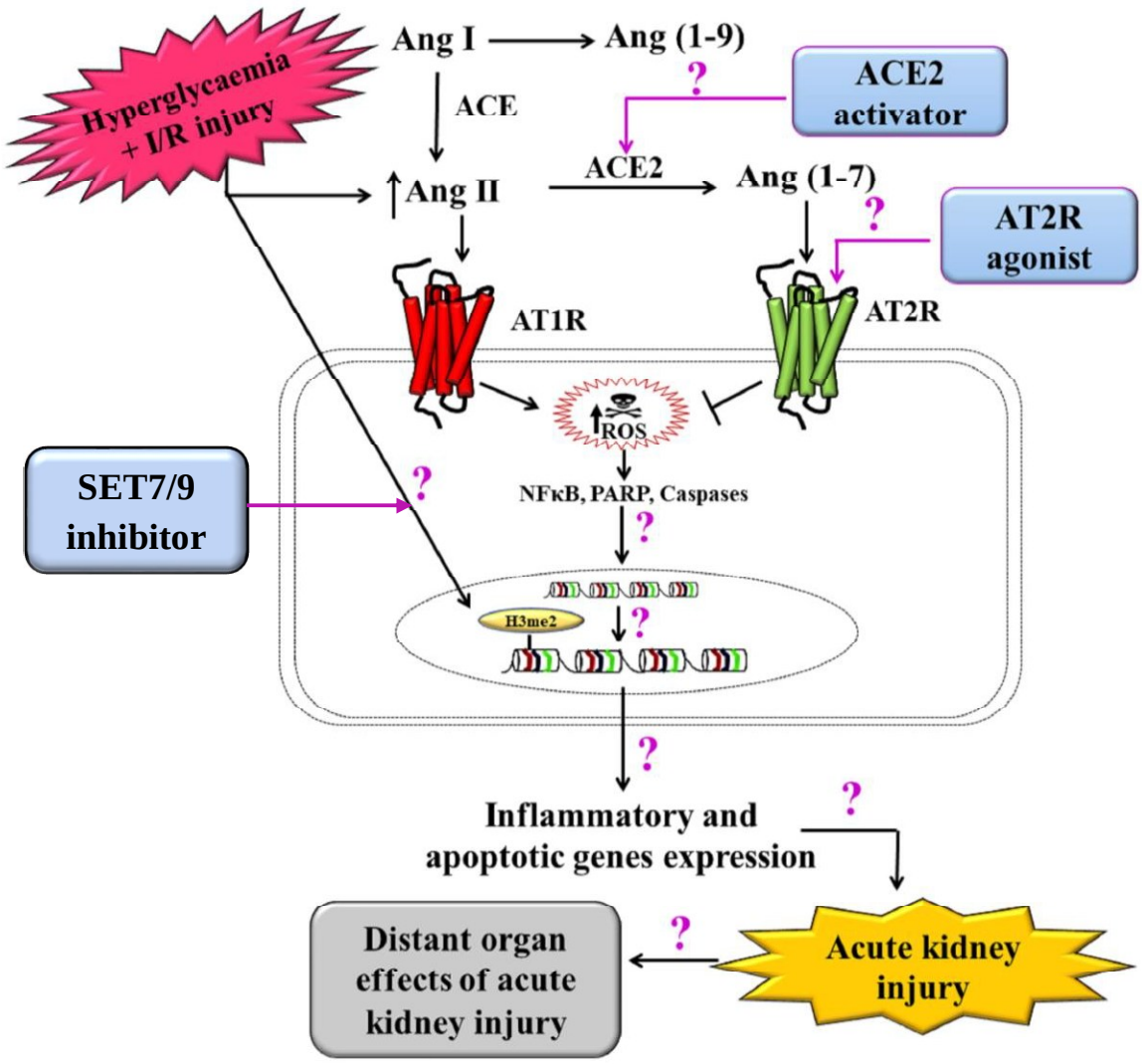

Figure 3.1 Gaps in existing research

In diabetes-AKI comorbidity, the role of histone methylation and depressor arm of RAS remains highly unclear. Targeting HMT-SET7/9 by its potent inhibitor might emerge as an epigenetic target for AKI treatment. On the other hand, activation of ACE2 and AT2R could provide novel opportunities to curb AKI and its associated distant organ dysfunction. HMT: histone methyltransferase, ACE2: Angiotensin-converting enzyme 2, AT2R: Angiotensin II type 2 receptor, I/R: Ischemia/reperfusion.

3.2. Objectives:

- To evaluate the role of epigenetics in the development of acute kidney injury under normal and hyperglycemic conditions.
- To study the role of AT2 receptor and ACE2 in the development of acute kidney injury under normal and hyperglycemic conditions.
- To study the multiple-organ dysfunction induced by acute kidney injury under normal and hyperglycemic conditions.