Anti-cancer tyrosine kinase inhibitors (TKI) are known to exert cardiotoxicity that can result in heart failure. Here we have used primary adult rat cardiac fibroblasts (CFs) to examine whether imatinib and sunitinib (both TKIs) increase oxidative stress and cause increased oxidation and activation of calcium/calmodulin dependent protein kinase II (CaMKII). Activation of CaMKII is known to be important for cellular function but excessive activation is linked to cardiac pathology.

CFs, isolated from adult Wistar rat hearts, were maintained in culture and treated over 24 hour with the TKIs sunitinib and imatinib (0.1–20 μM) in serum-free medium (DMEM). Cell phenotype and growth was monitored using a Nikon Eclipse (TE300) inverted microscope and ROS assays performed using a specially designed assay kit (Abcam, UK) which uses DCFDA to measure hydroxyl, peroxyl and other ROS activity. Quantitative immunoblotting was used to assess ox-CaMKII protein levels.

Treatment with both TKIs caused a dose-dependent decrease in cell viability. Sunitinib exerted more toxic effects at lower concentrations than imatinib. Decreased cell viability was evident at concentrations as low as 1 μM for sunitinib with dramatic cell loss (>50%) evident at 10–20 μM. Significantly increased ROS levels (using the DCFDA-based assay) were observed in the presence of both imatinib (4956±102 vs 1984±358 (sunitinib vs vehicle (a.u.)), n=3, p<0.01). Quantitative immunoblotting suggested that ox-CaMKII levels were increased following treatment with either 1 μM imatinib (1.4-fold (ox-CaMKII/GAPDH)) or 1 μM sunitinib (1.2-fold (ox-CaMKII/GAPDH)) however at higher concentrations (particularly for sunitinib) increased cell loss and resultant loss of total protein was observed. In conclusion, both imatinib and sunitinib cause increased oxidative stress in adult primary CFs with resultant activation of CaMKII. These effects are evident at lower concentrations of sunitinib than for imatinib and reflect the increased cardiotoxicity of this TKI reported in the patient.

Stem cell derived myogenic progeny play important roles in the pathophysiological processes of various vascular disorders, such as arteriosclerosis, atherosclerosis, and in-stent restenosis. Targeting these cells is an attractive therapeutic strategy for treating vascular remodelling. However, while polymer-coated DES have significantly reduced the incident of in-stent restenosis, current DESs lack the fundamental capacity for (i) adjustment of the drug dose and release kinetics and the (ii) ability to replenish the stent with a new drug on depletion. This limitation can be overcome by a strategy combining magnetic targeting via a uniform field-induced magnetization effect and a biocompatible magnetic nanoparticle (MNP) formulation designed for efficient entrapment and delivery of specific drugs that target the resident vascular stem cell source of the SMC. Magnetic nanoparticles (MNP’s) containing magnetite (Fe₃O₄) were fabricated, polymer coated with poly (DL-lactide-co-glycolide) polyvinyl alcohol [PLGA-PVA] and loaded with a γ-secretase inhibitor (GSI) of Notch signalling, DAPT using an oil in water emulsification technique. The free GSIs and GSI-loaded MNP’s were assessed for drug release, the efficacy at