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Diabetic endothelial colony forming cells have the potential for restoration with glycomimetics

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Endothelial colony forming progenitor cell (ECFC) function is compromised in diabetes, leading to poor vascular endothelial repair, which contributes to impaired diabetic foot ulcer healing. We have generated novel glycomimetic drugs with protective effects against endothelial dysfunction. We investigated the effect of glycomimetic C3 on the functional capacity of diabetic ECFCs. ECFCs were isolated from healthy controls and patients with diabetes with neuroischaemic (NI) or neuropathic (NP) foot ulcers. Functionally, diabetic ECFCs demonstrated delayed colony formation ($p < 0.02$), differential proliferative capacity ($p < 0.001$) and reduced NO bioavailability (NI ECFCs; $p < 0.05$). Chemokinetic migration and angiogenesis were also reduced in diabetic ECFCs ($p < 0.01$ and $p < 0.001$), and defects in wound closure and tube formation were apparent in NP ECFCs ($p < 0.01$). Differential patterns in mitochondrial activity were pronounced, with raised activity in NI and depressed activity in NP cells ($p < 0.05$). The application of glycomimetic improved scratch wound closure *in vitro* in patient ECFCs ($p < 0.01$), most significantly in NI cells ($p < 0.001$), where tube formation ($p < 0.05$) was also improved. We demonstrate restoration of the deficits in NI cells but not NP cells, using a novel glycomimetic agent, which may be advantageous for therapeutic cell transplantation or as a localised treatment for NI but not NP patients.

Diabetic foot ulceration is a chronic complication in diabetes where tissue damage occurs due to neuropathy, ischemia and/or infection[1] and given its resistance to treatment, provides the impetus for development of novel healing modalities. Chronic wounds are characterized by a persistent inflammatory phase, often complicated with infection, and a failure of defence cell response to damaging micro-environmental stimuli and often results in amputation[2]. One of the notable characteristics of diabetic macroangiopathy (DM), is the prevalence of coexistent coronary disease[3,4] and vascular calcification[5], which results in chronic limb ischemia (or CLI) caused by a compromised repair process and ultimately increases risk of mortality[4]. Despite the compromised angiogenic process in diabetes, associated with endothelial dysfunction and microvascular complications[6], stem or progenitor cell therapy shows promise for repair of ischemic tissue through neovascularisation[7]. A meta-analysis of studies using stem cell therapy, suggests enhanced diabetic foot ulcer healing and outcomes, reducing pain, lowering amputation rate and improving prognosis compared with standard treatment[8,9]. Although there reports demonstrate the impact of endothelial progenitor cells (EPC) in vascular regeneration[10–12], no studies have evaluated functional distinction between cells isolated from neuroischemic (NI) versus neuropathic (NP) patients.

Both NI and NP patients exhibit neuropathy, which may be caused by a breakdown in homeostatic metabolic and vascular factors, contributing to impaired wound healing through reduced oxygen delivery, nutrients and angiogenic growth factors[13]. The first part of this study aimed to determine whether distinctive differences could be identified between ECFCs isolated from patients with NI vs NP wounds, and establish whether this could contribute to impaired would healing.

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