content makes the silicate network more compact, thus modifying the reactivity of the glass, with an increasing Li^+ content causing a reduction in the matrix solubility consequently reducing the release of ions and delaying the formation of the apatite layer (Brückner et al., 2016). On the other hand, it has been demonstrated that ion release from Li-substituted BG can be tailored to induce an appropriate biological response (da Silva et al., 2017); for example, the partial replacement of Na_2O by up to 5 wt% of Li_2O in the 45S5 BG (Miguez-Pacheco et al., 2016) ensures the release of Li^+ within the therapeutic range for humans (0.5–1.2 mmol) (Mota de Freitas et al., 2016; Oruch et al., 2014).

7.2 ANGIOGENIC EFFECTS OF LITHIUM-CONTAINING BIOACTIVE GLASSES

7.2.1 In Vitro Evidence

A recent study showed that human umbilical vein endothelial cells (HUVECs) treated with ion dissolution products of 45S5 BG microparticles (<5 μm) containing 5 wt% of Li_2O (45S5.5Li) exhibit a proliferative and migratory response and have the capacity to form tubules in vitro (Haro Durand et al., 2017). In addition, the activation of the Wnt/β-catenin canonical pathway and an increase in the levels of expression of proangiogenic cytokines (IGF1 and TGF-β) were observed. The concentration of Li^+ released from 45S5.5Li microparticles (0.20 mmol) is in agreement with the findings of Miguez-Pacheco et al. (Miguez-Pacheco et al., 2016) using glass-ceramic scaffolds derived from the glass 45S5 with 2.5 and 5 wt% of Li_2O incubated in SBF. Similar results were recently obtained in our laboratory when incubating glass-ceramic scaffolds derived from 45S5.5Li BG in M199 medium (Haro Durand et al., 2016). It is important to note that the concentration of Li^+ released from the previously mentioned biomaterials is below the reported reference values at which cytotoxic effects are apparent (5–25 mmol) (Wu et al., 2014; Zeilbeck et al., 2014; Mao et al., 2001; Cheng et al., 2003; Struewing et al., 2009). However, Brückner et al. (2016) observed a higher release of Li^+ (5.5 mmol) from microparticles (<38 μm or 300–500 μm) of the glass 45S5 with 12.2% in moles of Li_2O incubated for 72 h in Tris buffer.

Fig. 7.1 shows that at 48 h poststimulation, a statistically significant increase in the proliferation of HUVECs treated with the M199 medium supplemented with the ionic dissolution products (IDPs) released from glass-ceramic scaffolds derived from 45S5.5Li BG (M199 + 45S5.5Li) was observed (Haro Durand et al., 2016).

In order to establish whether the presence of Li^+ in M199 medium enriched with the IDPs from scaffolds 45S5.5Li (M199 + 45S5.5Li) could account for the effect observed in the proliferative capacity of HUVECs, a proliferation assay with M199 medium enriched with LiCl was performed. The M199 medium supplemented with 0.60 mmol LiCl stimulated the in vitro proliferation of HUVECs, with no significant differences with the response observed with M199 + 45S5.5Li (Fig. 7.1).