pathway, as well as Li^+ protecting chondrocytes and cartilage tissues from the inflammatory environment through upregulation of the level of autophagy (Wu et al., 2014).

In a recent publication, Maçon et al. (2017) showed that when lithium citrate was used as a Li precursor, mesoporous glass containing Li as a network modifier was obtained, whereas the use of lithium nitrate produced relatively dense glass-ceramic with the presence of lithium metasilicate as a separate phase in the glass matrix, as shown by X-ray diffraction, magic angle spinning-solid state nuclear magnetic resonance (MAS NMR) spectroscopy, and nitrogen sorption data. Both glass- and glass-ceramic-released silica and Li^+ ions in culture media, but the release rate was lower for the glass-ceramic. Both samples did not affect chondrocyte viability and proliferation (Maçon et al., 2017).

The osteogenic potential of biocomposite scaffolds of Li-MBG and monomethoxy poly(ethylene glycol)-poly(D,L-lactide-*co*-glycolide)-poly(L-lysine) copolymer was also evaluated (Cai et al., 2015). The cell experimental results showed that cell attachment, proliferation, and alkaline phosphatase activity of MC3T3-E1 cells on biocomposite scaffolds of Li-MBG were remarkably improved as compared to control scaffolds. In animal assays, biocomposite scaffolds of Li-MBG promoted new bone formation (Cai et al., 2015).

7.4 SUMMARY AND FUTURE DIRECTIONS

The results summarized in this chapter demonstrate that HUVECs have greater migratory and proliferative response and ability to form tubules in vitro after stimulation with the IDPs of 45S5.5Li BG. Results also show the activation of the canonical Wnt/β-catenin pathway and the increase in the expression of proangiogenic cytokines (IGF1 and TGFβ). Exposure to IDPs of 45S5.5Li BG showed increased angiogenesis in vivo, as evidenced by the higher expression of the subunit *β3* of the integrin *αvβ3* and greater vascular density in quail embryo CAMs. This response was similar to that observed after the application of $10\,\mu g\,mL^{-1}$ bFGF. Therefore, the IDPs released from 45S5.5Li BG could act as inorganic angiogenic agents, thus representing a promising alternative to costly, delicate, and potentially harmful growth factors (Barrientos et al., 2014; Mitchell et al., 2016).

The stimulation of the angiogenic response could be due to the synergistic effect that determines the release of Si and Li^+ ions from microparticles and scaffolds of the bioactive glass 45S5.5Li on the production of proangiogenic cytokines (IGF1 and TGF-β) and activation of the Wnt/β-catenin canonical pathway. It has been previously described that the proangiogenic effects of TGF-β are associated with the expression of ALK1 receptors and with the activation of signaling cascades that trigger the proliferation and migration of endothelial cells via phosphorylation of Smad 1/5 (Lebrin et al., 2005; Goumans et al., 2009), and that IGF1 acts through the IGF1 receptor by activating the migration and tubulogenesis of endothelial cells through the Ras/Raf/ERK