transform stromal cells into CAFs, and CAFs secrete unique cytokines and growth factors, such as CXCL12, VEGF, PDGF, and hepatocyte growth factor (Plaks et al., 2015; De Palma et al., 2017). Co-culture with obese ASCs resulted in breast cancer cells having increased mesenchymal phenotype and proliferative capacity compared to those cultured with lean ASCs, indicating an increased capacity for tumor growth and metastasis. Due to CAFs' role in supporting tumor growth, it is critical to identify factors that contribute to the development of this population in the tumor microenvironment. Furthermore, there is substantial evidence demonstrating that CAFs are important regulators of the cancer immune response and promote immune evasion of cancer cells (Liu et al., 2019).

Obesity further promotes breast cancer tumorigenic potential by remodeling the extracellular matrix (ECM). Tumor-associated ASCs increase the expression and stiffness of fibronectin *via* mediation of secreted TGF-B in triple-negative breast cancer (Chandler et al., 2011). Seo et al. found that ASCs isolated from adipose tissue in obese versus lean mice create a stiffer matrix by promoting increased myofibroblast differentiation through mechanotransduction (Seo et al., 2015). This altered matrix contains increased concentrations of aligned collagen-1 and fibronectin fibers and can promote the malignant potential of mammary epithelial cells (Springer et al., 2019). Interstitial fibrosis associated with obesity also contributes to a phenotypic change in macrophages that resembles that of TAMs (Dunne et al., 2014). Bone marrow-derived macrophages cultured on obese versus lean ASC matrix have increased expression of anti-inflammatory macrophage (M2) markers CD206 and arginase-1 (Dunne et al., 2014). Furthermore, transcriptomic data indicate that macrophages from obese versus lean tumor-free human breast adipose have increased expression of genes that are associated with the TAM phenotype (Dunne et al., 2014). These data collectively suggest that obesity-associated ECM can promote tumorigenic potential by recapitulating characteristics of tumor-associated stroma.

ASCs IN NOVEL LABORATORY MODELS OF BREAST CANCER

3D Model Systems

In cancer research, *in vitro* 2D cell cultures are most commonly used for understanding cellular biology and morphology, as well as in pre-clinical drug trials (Jacoby and Pasten, 1979). However, there are many disadvantages and limitations with 2D cultures, such as no cell-to-extracellular interactions and cell morphology changes (Kapałczyńska et al., 2018). These limitations of 2D culture systems are addressed by 3D culture systems, because they more closely mimic the behavior of the cells in their natural environment: the human body. 3D cultures can be advantageous over 2D cultures in that these environmental niches are replicated. **Figure 2** summarizes the applications of ASCs in 3D laboratory

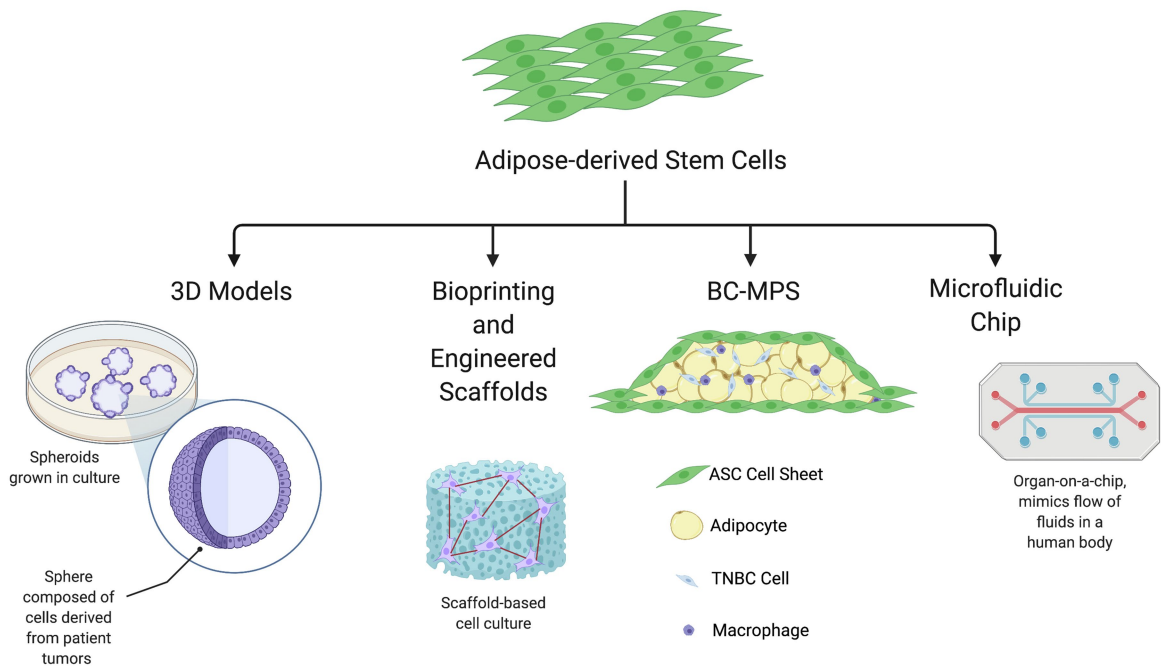

FIGURE 2 | Adipose-derived stem cells in translational research models. Adipocytes and ASCs have many applications in 3D laboratory models of breast cancer.

and provide both proliferative cues and drive carcinogenesis, especially in the context of obesity. Future directions into this area of research include using pharmacological or molecular inhibitors of downstream targets of ASCs to test their direct effects on cancer development and progression. We have described adipocytes and ASCs in novel laboratory models of breast cancer. Novel microphysiological systems enable more translational research of complicated cell-to-cell and cell-to-tissue interactions that occur in the human body. These 3D models can range from spheroids, 3D printed scaffolds or constructs, microphysiological systems to organ-on-a-chip systems, which are useful for studying the mechanisms behind cancer invasion and migration with implications for pharmaceutical discovery and targeted cancer therapy. Adipocytes and ASCs are also promising tools in cancer therapeutics and regenerative medicine, due to their plastic nature. Further investigation is required to ensure the safety of ASC use in tissue-engineered constructs and/or autologous grafting.

AUTHOR CONTRIBUTIONS

CB and KH wrote this manuscript with help of MA, MW, and TC. KH and GW created figures. KN and MSA contributed to the final revision of this manuscript. BC-B, BB, and MB contributed financially to the manuscript. All authors contributed to the article and approved the submitted version.

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