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MESENCHYMAL STEM CELL DERIVED SMALL EXTRACELLULAR VESICLES TO FACILITATE REPAIR OF ANASTOMOTIC LEAKAGE

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Anastomotic Leakage (AL) can be defined as an abnormal wound of the intestinal wall at the site of anastomosis resulting in continuity between the intra- and extraluminal compartments. Post-surgical AL continues to represent a serious and often fatal complication following gastrointestinal procedures, leading to extended illness, increased death rates, and a major strain on healthcare systems. Current clinical practice largely deals with the consequences of AL rather than addressing its root causes. Our objective is to shift the therapeutic paradigm from reactive treatment to true prevention. Rather than waiting for AL to develop and then managing its consequences, we aim to prove that Mesencymal Stem Cell derived small Extracellular Vesicles (MSC-sEVs) can preemptively repair the healing process and stop AL at its source.

We carried out a comprehensive review of 15 scientific articles spanning from the years 2017 to 2025. We systematically examined previously published studies to assess the therapeutic potential of MSC-sEVs in anastomotic repair. MSC-sEVs contribute to anastomotic healing largely through powerful regulation of immune responses during the initial inflammatory stage of tissue repair. Following an anastomotic procedure particularly in case of acute obstruction, tissue restoration is compromised due to hyperactivation of immune cells. These nanometer-sized vesicles suppress overactive pro-inflammatory cascades, including the IL-17, NF-κB, and TNF pathways. As a consequence, they reduce neutrophil recruitment, limit M1-type macrophage activation, and prevent the buildup of Th17 cells known to be major IL-17 producers at the surgical junction, thus disturbing the vicious cycle of inflammation that sustain tissue destruction. At the same time, MSC-sEVs encourage anti-inflammatory signals such as M2 macrophage differentiation and elevated levels of IL-10 and IL-13. Beyond immune control, MSC-sEVs carry bioactive molecules like miR-136-5p and Wnt4 that stimulate local cell regeneration. They also promote intestinal healing by driving epithelial cell movement and multiplication, restoring the mucosal barrier. Additional benefits include activation of the PTEN/AKT pathway that promotes angiogenesis, a process essential for delivering oxygen and nutrients to the metabolically demanding repair site. Additionally MSC-sEVs help preservation of goblet cells, the specialized epithelial cells responsible for secreting the protective mucus layer that shields the intestinal lining from luminal contents.

Moreover, a newer area of interest concerns how MSC-sEV therapy might interact with gut bacteria. Bowel obstruction, which often leads to anastomotic leakage, does more than just obstruction, it also cause dysbiosis, reducing the bacterial diversity, increasing harmful microbes like *Bacteroides vulgatus*, and decreases helpful ones such as *Lactobacillus intestinalis*. This microbial imbalance can weaken the gut barrier, worsen inflammation, and increase the risk of anastomotic failure. Although we still lack direct proof that MSC-sEVs can restore this balance, it is a promising direction for future research, since better immune control at the surgical site may indirectly support a healthier microbial environment.

In conclusion, based on our analysis of the available literature, MSC-sEVs hold significant promise as a novel cell-free therapeutic approach that targets the early inflammatory events leading to AL, rather than simply managing its late complications. Future work should focus on standardizing production protocols, evaluating safety and efficacy in large-animal models, and initiating early-phase human trials to test clinical applicability in high-risk surgical patients.