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Ovarian Stroma: Follicle Activation Regulator

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For decades, reproductive science has been "follicle-focused," a perspective driven by the central biological role of the germ cell in determining female reproductive lifespan. We have long treated the primordial follicle (PMF) as an isolated biological unit, often overlooking the complex structural composition of its surrounding ovarian stroma. This perspective is shifting. Increased evidence indicates that the ovarian stroma is far from a passive structural scaffold. Instead, it functions as an active regulatory component of the follicular niche.

This shift in understanding is driven by research showing that follicle depletion is not just a natural cellular decay, but a process strongly influenced by the stroma's mechanical and molecular state. Kalich-Philosoph et al. (2013) demonstrated that chemotherapy induces a “burnout” effect by prematurely activating dormant follicles through intrinsic and extrinsic regulatory pathways. This follicle loss is further worsened by structural injury to the ovarian cortex. As observed by Meirow et al. (2007), chemotherapy triggers focal fibrosis and vascular damage that compromises the stromal environment. Roness et al. (2016) further confirmed that this damage, including vascular injury and indirect toxicity, accelerate follicles loss.

This regulatory role of the stroma is critical during ovarian tissue transplantation (OTT). Gavish et al. (2018) reported that OTT leads to massive early follicle loss because the stromal mechanisms that maintain dormancy, such as matrix stiffness, are compromised during the graft process, leading to accelerated follicle activation and loss. Stromal disruption triggers follicle activation surge by suppressing Hippo signalling, which functions as an inhibitor pathway (2025). The mechanical basis was further clarified by Nagamatsu et al. (2019), who found that physical stress from the extracellular matrix (ECM) induces oocyte nuclear rotation, retaining FOXO3 in the nucleus and maintaining follicular quiescence. When the stromal microenvironment is disrupted or becomes fibrotic, physical compression is lost, FOXO3 nuclear export is promoted, and follicle activation is triggered. Because this mechanical failure is involved in the follicle loss, Roness and Meirow (2019) concluded that improving graft survival requires new strategies that stabilize the follicular niche and protect the stroma to prevent follicle over activation and burnout.

At the cellular and molecular level, Spector et al. (2024) demonstrated AMH receptor expression on ovarian stromal fibroblasts with functional post-receptor activity. This suggests that the stroma can regulate follicle activation through AMH mediated signalling.

This perspective is reinforced by the work of Wang and Yang (2025) and Félix and Silva (2025), which establishes the stroma as a mechanical regulator where the physical stiffness and structural density of the ECM act as a functional gatekeeper of follicle dormancy. Furthermore, Edepli and Yaba (2025)

elucidated the molecular pathways driving the fibrotic process, characterizing how ovarian fibrosis and pathological ECM deposition create a rigid environment that disrupts normal signalling. By translating biomechanical tension into intracellular pathways, these findings collectively suggest that follicle fate is dictated not only by intrinsic follicle factors but also by the dynamic physical, biochemical, and molecular state of the surrounding stroma.

Modern reproductive medicine should therefore focus not only on restoring follicular function but also on preserving a healthy stromal environment to prevent infertility and optimize clinical outcomes. This is especially important when gonadotoxic chemotherapy, autoimmune diseases, or inflammation induce pathological premature massive activation of resting follicles resulting in a “burnout”, leading to premature ovarian reserve depletion. Emerging insights provide a basis for next-generation therapies in which modulation of the ovarian stroma enables targeted control of follicular dynamics. Taken together, these findings suggest that modulation of the stromal microenvironment, including its structural organization, ECM composition, and stromal cell signalling pathways, may optimize both in vitro maturation (IVM) and OTT through controlled regulation of the equilibrium between follicular activation and quiescence.

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