Therapeutic manipulations for POI: will yapping awaken the sleepy follicle?

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Traditional etymologies aside, the flurry of acronyms that have invaded the scientific and medical vernacular of today continues to overwhelm the literature with terminology we desperately attempt to keep up with. Our new lexicon reads more like a litany of MADs, Tolls, Gremlins, HIPPOs and other assorted characters reflecting specific genes and their protein products. The privilege of naming your favorite molecular entity in most cases arose from the unveiling of gene function in experimentally tractable model organisms like *Drosophila* and their compatriots. Enter YAPs into the schemata of reproductive medicine.

Assigning names to these genes and their products falls under the purview of their discoverers, with the final choice of acronym being a byproduct of “need” and something catchy and possibly tied to what this molecule actually does within the context of living cells or tissues. As discussed below, YAP is a moniker applied to proteins involved with the regulation of organ size. A quick Google search reminds us that YAP connotes “of a dog, to bark in high quick sounds...to talk in a loud and annoying way.” And if you are the proud owner of Pomeranians (as my wife is), you know exactly what I mean when an episode of yapping occurs in the middle of the night!

One of the most challenging and unsolved problems in reproductive biology and medicine concerns the deposition and utilization of the ovarian follicle reserve. It lies at the heart of what determines the reproductive lifespan for women and for many sets the stage for the likelihood of having children with or without ARTs. For women diagnosed with premature

ovarian insufficiency (POI), due to an inability to sustain an adequate ovarian reserve into that stage of adulthood when childbearing would be desired, there is little hope, especially given the early age at which follicle depletion is detected. And, given the increased survivorship of patients who undergo ovotoxic medical treatments, POI is sadly affecting a growing number of individuals who will seek options provided by fertility preservation strategies. A breakthrough paper recently published in PNAS is offering new hope for the treatment of POI.

Built on a sound and provocative basic science foundation, the study coming from the laboratories of Dr. Aaron Hsueh at Stanford University and Dr. Kazuhiro Kawamura at St. Marianna University School of Medicine brings into focus the role of YAP in the control of ovarian follicle dynamics (Kawamura, K., et al., *Hippo signaling disruption and Akt stimulation of ovarian follicles for infertility treatment*. www.pnas.org/cgi/doi/10.1073/pnas.1312830110). Moreover, deploying cues gleaned from experiments with rodent models, Hsueh and his colleagues in Japan cleverly translate their mechanistic insights by applying a derivative treatment paradigm for a group of POI patients that has thus far resulted in the birth of a baby boy. This accomplishment is garnering attention from basic science and clinical communities alike not only for its proof-of-principle value but also because the birth is the first following the utilization of vitrified ovarian tissue.

As first reported by Hsueh at the NICHD-ASRM workshop a year ago (see JARG (2013) 30:285–292, doi [10.1007/s10815-013-9968-2](https://doi.org/10.1007/s10815-013-9968-2)), fragmentation of mouse ovaries was found to stimulate the production of growth factors that directed follicle development sufficient to support the production of mature oocytes. Probing this response to tissue disruption more deeply revealed enhanced polymerization of actin was linked to inactivation of the Hippo signaling pathway involving the redistribution of YAP from the cytoplasm to nucleus of granulosa cells of primary and secondary follicles within 4 h of

Capsule A recent study translates new insights regarding the molecular underpinnings of follicle development from mice to humans that may provide a therapeutic intervention for Premature Ovarian Insufficiency (POI).

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ovarian mincing. The shuttling of transcription factors between nuclear and cytoplasmic compartments is well-known to be a rate-limiting event in selective gene activation in many developing systems and here was shown to evoke up-regulation of CCN growth factors and inhibitors of apoptosis capable of enhancing both follicle growth and survival. Central to this growth-promoting effect was the use of an inhibitor of YAP to sustain follicle growth. When this condition was further embellished using stimulation of the Akt signaling pathway, already implicated in the process of follicle activation, and ovarian fragments were grafted into recipient mice, a significant and robust response to ovarian development was observed promoting extension of these studies to the human ovary.

The paradigm described above was essentially recapitulated using cubes of ovarian tissue and after grafting to immunodeficient mice, antral follicle development was detected in as little as 4 weeks following grafting. With such a promising result in hand, investigations were extended to a group of POI patients who had an ovary removed and underwent vitrification of cortical ovarian strips. 13 patients displayed sufficient numbers of follicles upon thawing and fragmentation. Following 2 days of treatment with Akt activators, tissue cubes were autografted to the Fallopian tube serosa, and patients were monitored for signs of ovarian activity. Controlled ovarian hyperstimulation resulted in the successful retrieval of oocytes from 5 patients that were fertilized by ICSI and frozen at the 4-cell stage. From one of these patients, a healthy child was born.

Three notable conclusions are evidenced by this work. First, a fundamental inquiry into the consequences of tissue disruption and the causes of follicle activation and sustained growth in the mouse has uncovered a previously unknown link between YAP and the Hippo signaling pathway that can

be exploited to obtain fully developed oocytes with developmental potential. While questions remain as to the means by which actin polymerization mediates the changes in YAP localization, there is abundant evidence in the cell biology literature implicating cytoskeletal stability in the trafficking of transcription factors into and out of the nucleus that may suggest further avenues for optimizing this technology in animal and human studies. Second, the translation of a mechanistic insight from mouse to human implies the existence a highly conserved pathway operative within the ovarian follicle that potentially could be exploited to avert and/or avoid the intrinsic loss of follicles that accompanies advancing maternal age or disease conditions like POI. Finally, the modifications of existing approaches for fertility preservation, namely vitrification and the use of smaller disrupted-drug-treated pieces of tissue, open new possibilities for improving what have thus far been the limited number of successful cases resulting in birth of live young or the restoration of ovarian physiology from a previously menopausal state.

It is in this context that we draw the attention of our readership to the lead paper in this issue of JARG entitled “In vitro development of primordial follicles to preantral stage following vitrification” contributed by Khosravi and colleagues from Queen’s University in Kingston, Ontario. This study describes the successful modification of a vitrification system for human cortical strips to achieve antral follicle development over a 7-day culture period. The work melds nicely with the report from Kawamura et al., and reinforces the commitment of JARG to both inspire the field of fertility preservation as a clinically acceptable form of human ART and to bring the frontline advances of technology and reproductive biology to our readership.