Is it in our patients' blood? On a quest for predictors of blastocysts' aneuploidy rate

In the article "Shorter telomere length of white blood cells is associated with higher rates of aneuploidy in infertile women undergoing in vitro fertilization," Hanson et al. (1) reported an association between the length of white blood cells' (WBCs) telomeres and aneuploidy rate per biopsied blastocysts among 175 infertile women. Apparently, shorter the telomeres, higher the risk of chromosomal missegregation. A recurrent scenario also exists based on studies investigating other branches of medicine, where shorter/longer WBCs' telomeres were prognostic for pathologies like cardiovascular diseases and cancer. Yet, a common drawback is the large variability of the WBCs' telomere length across individuals and their large dynamicity even in the same individual over a period of time. When Hanson et al. (1) analyzed the same feature for cumulus cells' (CCs') telomeres, no association with blastocysts' aneuploidy rate was identified. The study has some limitations, largely highlighted by the investigators themselves: the high rate of inconclusive results; analysis of CCs pooled from cohorts of cumuli rather than single ones; and absence of a significant association when the data were adjusted for maternal age. Hanson et al. (1) did a great job shedding light on this interesting topic, which certainly deserves further insights in the future.

Hanson et al.'s (1) data unveil substantially high variability in their distribution across maternal age for WBCs' and CCs' telomere lengths, suggesting that a yet unknown feature might subcluster these patients a priori. A scenario that becomes even more intriguing is whether the WBCs' telomere lengths can be confirmed based on future studies to be significantly associated with an equally, largely scattered outcome, such as the aneuploidy rate itself, among women of the same age. In fact, WBCs can be a easily analyzed from peripheral blood collections as opposed to blastocysts' aneuploidies, which are unpredictable unless preimplantation genetic testing for aneuploidies is performed. Future thorough analyses of a putative genetic predisposition/environmental effector involving aneuploidy outcomes higher/lower than expected are much needed. Such a theoretical predisposition was recently explored for oocyte quantity issues (e.g., diminished ovarian reserved and premature menopause) (2, 3). Thus, it is reasonable to start similar investigations on oocyte quality (i.e., fertilization, blastulation, aneuploidies, and implantation); additionally, Hanson et al. (1) themselves aimed at conducting this research. From a clinical perspective, this knowledge would be extremely precious for counseling and conceiving patient-tailored in vitro fertilization (IVF) treatments and strategies.

Focusing on the biological insights arising from their data, Hanson et al. (1) stated that "it appears that the follicular environment is unique and CCs possess mechanisms which are distinct from other somatic tissues." In fact, CCs, although characterized by an equally scattered distribution of the data across all different patients, showed longer telomeres than WBCs and their length was totally independent of maternal age. Recently, Olsen et al. (4) rather analyzed the epigenetic profile of the follicle somatic compartment. They also reported a distinctive signature, which was inconsistent with what was expected on the basis of maternal chronological age (i.e., younger) but was characterized by more epimutations and age-differentially methylated regions compared with other somatic cells. This fascinating peculiarity of the follicle incites further in-depth analyses of its molecular, physiological, and mechanobiological properties in the future. Evidence that has emerged from the literature has confirmed that CC's telomere length cannot discriminate competent oocytes from incompetent oocytes, and Hanson et al.'s (1) study excludes an association with blastocysts' chromosomal constitution. In other terms, these companion cells of the oocyte, i.e., one of the biggest and, certainly, evolutionarily most important cells, seem to be programmed to provide it with energetic support independent of their intrinsic developmental, chromosomal, or reproductive competence. Perhaps other CCs' features contribute to the acquisition of these qualities. For instance, rather than the length of the telomeres, Wang et al. (5) reported telomerase activity in follicular cells as a predictor of the chance to conceive after IVF.

In conclusion, Hanson et al. (1) have the merit of opening a window on this fascinating topic. Immunology, hematology, and genomics, just like bioinformatics and bioengineering, are contaminating the field of reproductive medicine, and soon, they will provide us with more efficient comprehensive prognostic tools to better tailor IVF treatments based on each woman's specific profile. Several pieces of information are written in our patients' genome, and others can be read in their blood, therefore we must keep trying to interpret these small pieces of the puzzle with a holistic perspective.

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