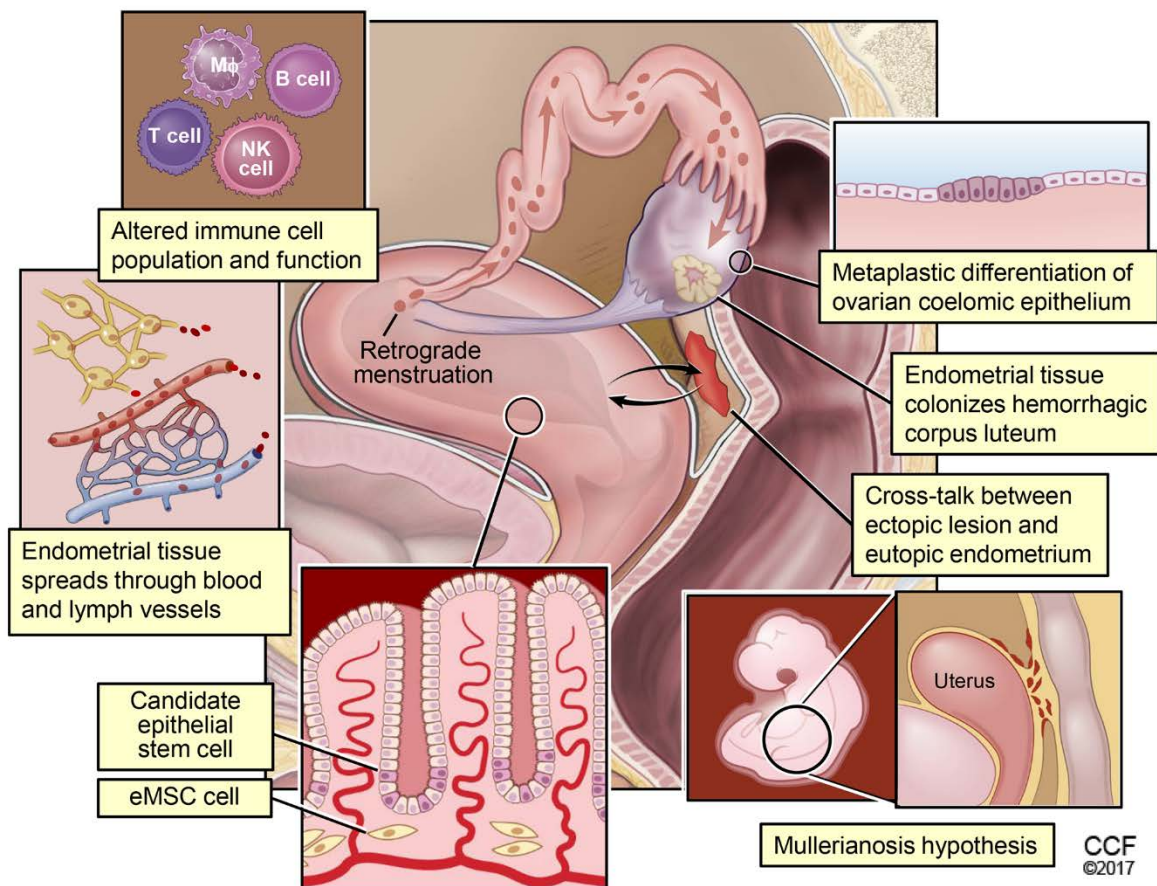
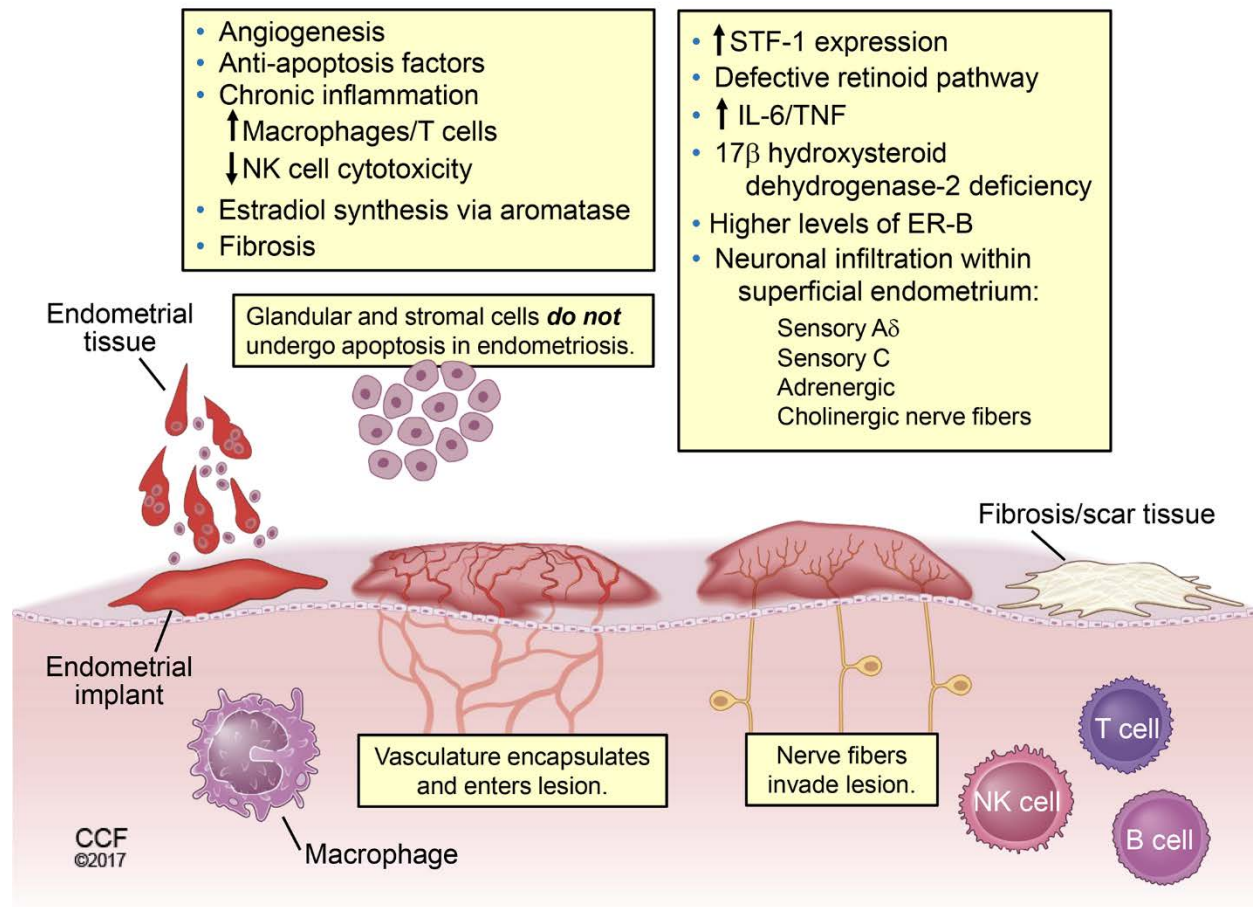


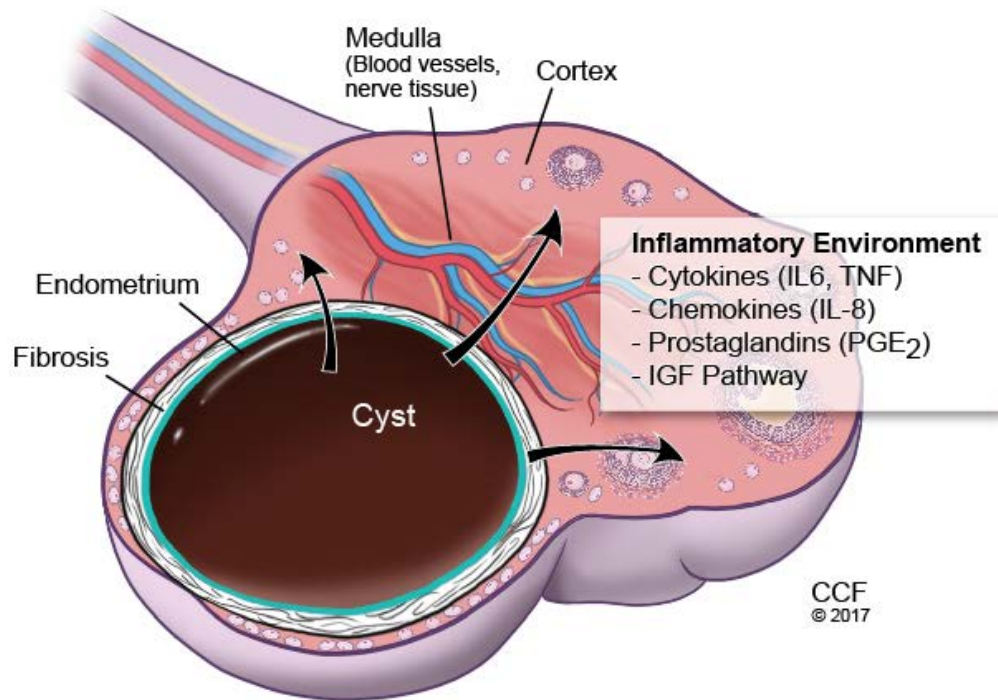
**Appendix 1. The most common proposed theory of retrograde menstruation deposited onto the peritoneal surface is shown in the central figure. Other contributing rather than competing hypotheses are depicted in this figure in a clockwise direction starting at the bottom left: 1) candidate endometrial epithelial progenitor cells and endometrial mesenchymal stromal–stem-like cells (eMSC) may possess a greater propensity to avoid clearance, attach and invade ectopic locations; 2) metastatic spread of endometrial tissue through blood vasculature and lymphatic channels; 3) altered immune cell population and functionality; 4) metaplastic differentiation of ovarian coelomic epithelium and invagination; 5) refluxed endometrial tissue trapped between the pelvic sidewall adhesions and ovary that then colonizes a hemorrhagic corpus luteum; 6) rectovaginal Müllerian remnant; and 7) Müllerianosis hypothesis of embryonic endometrial tissue ectopically placed during organogenesis. NK, natural killer. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2017. All Rights Reserved.**



**Appendix 2. Molecular mechanisms contributing to the development of endometriosis phenotypes. The most critical are chronic inflammation and neuronal infiltration. NK, natural killer; TNF, tumor necrosis factor. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2017. All Rights Reserved.**



**Appendix 3. The presence of an endometrioma leads to an inflammatory environment that may impact oocyte quality. The anatomic relationship to the cortex that contains follicles as well as the proximity to the vasculature of the ovary has surgical implications. IGF, insulin-like growth factor. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2017. All Rights Reserved.**



**Appendix 4. Central sensitization pathway. Peripheral sensitization (*red asterisks*) occurs at the site of the lesion with enhanced afferent (*purple*) and efferent (*orange*) signaling both locally and with the spinal cord. The *red dashed lines* represent new axon growth at the site of the lesion. In central sensitization (*red asterisks*), sensory afferents from the lesions and the pelvic floor coalesce within the sacral spine and can become independent of peripheral input. In this manner, myofascial pain can both develop from and also drive central sensitization. Numerous ascending and descending connections at each level of the central nervous system (CNS), including the brain are then influenced. Structural and functional changes in CNS neurons have tonic activation and may be hyper-responsive to even mild stimuli. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2017. All Rights Reserved.**

