

Infertility in Fabry's disease: role of hypoxia and inflammation in determining testicular damage

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Fabry's disease (FD) is a genetic X-linked systemic and progressive rare disease, which is characterized by the accumulation of glycolipid bodies (GB) into the lysosomes of almost all cell types and consequently by a multifiform clinical picture.

Here we studied testicular biopsies of a 42 ys old FD patient, presenting infertility with reduced number of spermatozoa and preserved sexual activity.

Testicular biopsies have been analyzed by optical microscopy (OM) and transmission electron microscopy (TEM). OM, showed a severe involvement of testis interstitium blood vessels with reduced or closed lumen, an increased of connective tissue and a substantial thickening of peritubular region. TEM, showed that GB were abundant in vessel wall cells and in myofibroblast of peritubular region. In contrast with literature reports, Leydig cells were constantly unaffected by GB accumulation showing well preserved ultrastructural organization. On the contrary, tubular cells, although not affected by GB accumulation, appeared severely damaged.

These data led us to hypothesize that diffusion of oxygen and nutrients from blood to tubules could be impaired.

To test this hypothesis we explored, by immunofluorescence (IF) and molecular biology (MB) coupled to laser capture micro-dissection (LCMD), the activation of HIF/NFκB pathway.

IF showed increased signal for HIF1α in all stromal components, while it appeared almost absent in seminiferous tubules. On the contrary, NFκB fluorescence was evident in tubules.

mRNA of tubular and interstitial tissue fractions, separately extracted by LCMD, confirms that HIF1α and hypoxic-related genes such as alarmin receptors (RAGE, TLR4) were overexpressed in the interstitial cells. At the same time, NFκB and a number of proinflammatory genes such as HMOX1, PTGES, SAA1-SAA2 were up-regulated in the tubule microenvironment.

Taken together, these results suggest that the GB accumulation in interstitium, reducing vessel lumen and increasing the distance between vessel and tubular cells, leads to chronic progressive hypoxia. Hypoxia has two effects: 1) Necrosis of cells more distant from vessels, especially germinative epithelium and Sertoli cells, releasing alarmins; 2) Adaptation to low levels of O₂, with activation of HIF1α. In both cases a strong activation of NFκB occurs that trigger a inflammatory response (IR). We suggest a role for the IR activation in determining intratubular cells damage and consequently, infertility in FD.