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Stem Cell Secreted Factors-Enriched Plasma Promotes DNA Repair and Protects Against Chemotherapy-Induced Cell Death in Ovarian Tissue.

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Abstract:

Introduction: Bone marrow-derived stem cells promoted fertility rescue and niche regeneration through the secretion of soluble factors in chemotherapy-induced ovarian damage mouse models. However, the underlying mechanisms remain unknown. Thus, we aimed to assess if stem cell secreted factors-enriched human plasma, obtained after mobilization with granulocyte colony stimulating factor (G-CSF), prevents DNA damage and/or promotes DNA repair in ovarian tissue.

Methods: Six-week old CD1 mouse ovaries were isolated and cultured for 24h with supplemented α-MEM medium. Samples were then randomized to the following experimental conditions (n=3/group): 1) Chemotherapy (ChT) group: treated with 1.2µm 4-hydroperoxy cyclophosphamide+0.12µM busulphan; 2) Control-plasma group: treated with ChT and peripheral blood plasma; 3) G-CSF group: treated with ChT and G-CSF plasma. Ovaries were collected at 12h or 24h and pooled to analyze DNA damage by western blot (H2AX, Bax, Bcl2 and cleaved caspase 3) and DNA repair by RT-qPCR (ATM, p53, Rad51, Apex1).

Results: G-CSF plasma increased the expression of DNA repair related genes at 12h when compared to ChT group. Furthermore, decreased the Bax/Bcl2 ratio (ChT 0.9 vs. G-CSF 0.7) and reduced cleaved caspase 3 (CC3) levels. A decline in the DNA damage markers, H2AX and CC3, followed by a reduction in the DNA repair genes was detected in the G-CSF treated ovaries when compared to ChT group at 24h. Interestingly, peripheral blood plasma also seemed to induce positive effects on DNA repair, although were not as relevant as those described for the G-CSF (Table 1).

Conclusion: Stem cell secreted factors-enriched plasma increased DNA repair reducing the pro-apoptotic signaling and cell death by apoptosis at 12h. These effects resulted in less DNA damage at 24h. Our study suggest that G-CSF plasma works by promoting DNA repair avoiding the chemotherapy-induced cell death.

Funded by the PROMETEO/2018/137 grant - Valencian Regional Government table_Table 1. Gene/protein expression

Gene/protein expression

	Gene/protein	12h			24h		
		ChT	Control plasma	G-CSF	ChT	Control plasma	G-CSF
Relative gene expression (fold change)	ATM	1.0	1.6	2.9	1.0	$7x10^{-3}$	0.2
	p53	1.0	1.0	2.2	1.0	7x10-3	2x10-3
	Rad51	1.0	3.0	9.4	1.0	7x10-3	2x10-3
	Apex1	1.0	1.1	2.4	1.0	9x10-3	3x10-3
Relative protein expression	H2AX	2.1	1.0	1.8	1.5	1.0	0.7
	Bax	0.4	0.3	0.1	0.4	0.1	0.2
	Bcl2	0.5	0.3	0.2	0.4	0.6	0.4
	CC3	2.8	1.6	0.4	0.8	0.5	0.4

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Category (Complete): 11.3 - Basic Reproductive Biology: Ovarian Biology, Reproductive Aging

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