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Sommario	Embryonic stem cells (ESCs) are characterized by a rapid cell cycle, which leads to high replication stress (RS) in otherwise unperturbed conditions. The mechanisms that ESCs adopt to cope with their endogenous RS, however, remain to this day elusive. In our recent work we demonstrated that the activation of the checkpoint kinase ATR in response to RS leads to a broad activation of 2-cells stage specific genes in mouse ESCs. This response relies on the up-regulation of Dux, a transcription factor encoded in a macrosatellite sequence repeated in tandem. Dux is repressed by variant Polycomb repressive complex 1 (vPRC1) in unperturbed ESCs, independently from PRC2 presence. Here we demonstrate that RS causes a major rearrangement of both PRC1 and PRC2 in ESCs nuclei, resulting in a major loss of both repressive marks in correspondence to target promoters. Surprisingly, Dux undergoes an increase in vPRC1 occupancy upon RS in an ATR-dependent manner, possibly due to PRC1 involvement in the replication of highly repeated DNA sequences. More interestingly, Dux activation upon RS requires the presence of PRC2. This result is possibly due to PRC2 proved role in the processing of stalled replication forks, which are the main structure signaling RS. In agreement to this data, also the fork

	remodeling translocases HLTF and ZRANB3 displayed an effect in Dux activation following RS. Taken together, our results show that the up-regulation of 2-cells genes following RS not only requires ATR activation, but also downstream remodeling processes.
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