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Doxorubicin anti-tumor mechanisms include Hsp60 post-translational modifications leading to the Hsp60/p53 complex dissociation and instauration of replicative senescence

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Hsp60 is a pro-carcinogenic chaperonin in certain tumor types by interfering with apoptosis and with tumor cell death. In these tumors, it is not known whether or not doxorubicin anti-tumor effects include a blockage of the pro-carcinogenic action of this protein. We used the human lung mucoepidermoid cell line NCI-H292 and different doses of doxorubicin to measure cell viability, cell cycle progression, cell senescence indicators, Hsp60 levels and its post-translational modifications as well as the release of the chaperonin into the extracellular environment. Cell viability was reduced in relation to doxorubicin dose and this was paralleled by the appearance of cell senescence markers. Concomitantly, intracellular Hsp60 levels decreased while its acetylation levels increased. The data suggest that Hsp60 acetylation may interfere with the formation of the Hsp60/p53 complex and/or promote its dissociation, both causing an increase in the levels of free p53, which can then activate cell senescence. On the other hand, acetylated Hsp60 is ubiquitinated and degraded and, thus, the anti-apoptotic effect of Hsp60 is impaired with subsequent tumor cell death.

References

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Keywords

Doxorubicin; Hsp60; p53; replicative senescence; post-translational modifications.