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Chaperonopathies and chaperonotherapy. Hsp60 as therapeutic target in cancer: potential benefits and risks.

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### Abstract

In this minireview we focus on Hsp60 as a target for anticancer therapy. We discuss the new concepts of chaperonopathies and chaperonotherapy and present information on Hsp60 localization in the cell membrane of human tumor cells. We describe novel mechanisms for Hsp60 reaching the extracellular environment that involve membrane-associated stages, as well as data on anti-Hsp60 antibodies found in human sera, both in normal subjects and patients affected by autoimmune diseases. Finally, we discuss possible therapeutic applications of anti-Hsp60 antibodies in cancer treatment, evaluating also side effects on non-tumor cells. In conclusion, the way for investigating Hsp60-targeted anti-tumor therapy is open, at least for those tumors that express Hsp60 on its surface and/or secrete it outside the cell, as is the search for the molecular mechanisms involved in Hsp60 translocation from cytosol to cell membrane: elucidation of this mechanism will greatly facilitate the optimization of chaperonotherapy centered on Hsp60 with anti-tumor efficacy and minimal side effects.

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## Supplement:

Hsp60: a key clinicopathologic factor and a promising target for therapeutics

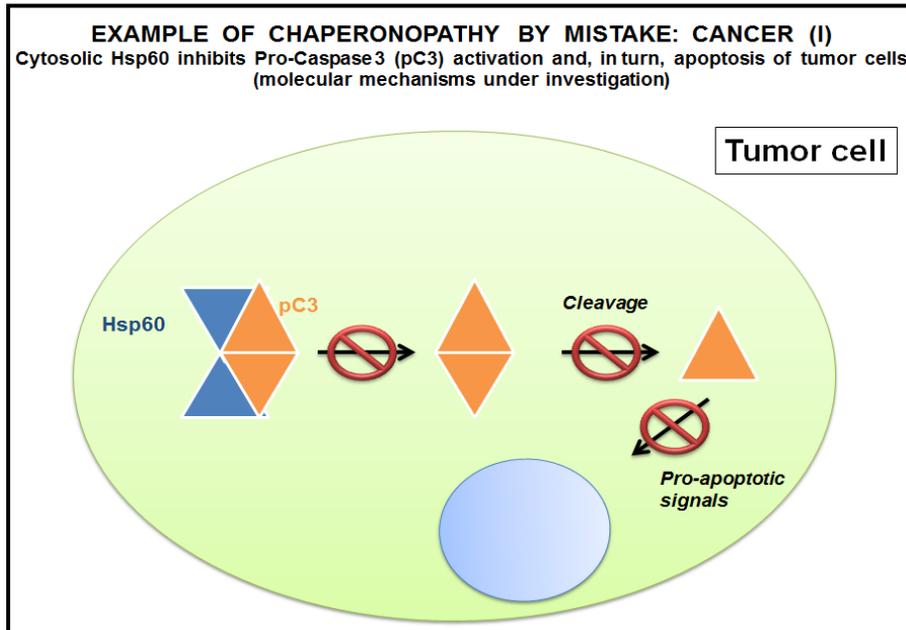
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Molecular chaperones have important physiological functions but they may also act as etiologic-pathogenic factors in a wide variety of pathological conditions. These diseases in which molecular chaperones play a role in the initiation, progression, and/or maintenance of the pathologic manifestations in cells and tissues are the chaperonopathies [1]. Some types of cancer belong to this category because one or more chaperones are essential for cancer cell growth and proliferation, and/or dissemination, and/or resistance to chemo and other forms of therapy. For example, Hsp60 is a chaperone that can “help” some tumors in various ways rather than protect the host from carcinogenesis (Figures 1 and 2). This is why this type of Hsp60 pathology is named chaperonopathy by mistake: a normal (or apparently normal according to the methods available today for studying molecular details) is “mistakenly” aiding the enemy, i.e., the cancer cell. There are other several examples of chaperonopathies by mistake pertaining not only to Hsp60 but also to other chaperones, e.g., Hsp70, Hsp90, sHsp, etc., and pertaining not only to cancer but also to other disorders such as chronic inflammation and autoimmunity [1]. In all these instances, it is appropriate to consider developing agents to block the pathogenic action of the chaperone. This would be an example of negative chaperonotherapy, which is the opposite of positive chaperonotherapy. The latter consists of complementation, or replacement, or activation of defective chaperones, of which there are numerous examples of considerable clinical relevance [1]. Hsp60 can be defective because of genetic mutation, or because of post-translational modifications, and can thus cause disease. These Hsp60 chaperonopathies are, in principle, candidates for positive chaperonotherapy. In conclusion, Hsp60 has many roles and its malfunctioning may cause disease, which makes the chaperonin a promising target for therapeutics in a variety of disorders, many of which are highly prevalent and serious.

[1] Macario AJL, Conway de Macario, E., and Cappello, F (2013) “The Chaperonopathies. Diseases with defective molecular chaperones.” <http://dx.doi.org/10.1007/978-94-007-4667-1>. ISSN 2211-9353; ISBN 978-94-007-4666-4; ISSN 2211-9361 (electronic); ISBN 978-94-007-4667-1 (eBook); Springer Dordrecht Heidelberg New York London. <http://www.springer.com/biomed/book/978-94-007-4666-4>

Picture 1:



Picture 2:

