Commentary

MAY HSP60 AND HSP10 EXPRESSION DURING LUNG CARCINOGENESIS CONFIRM THE "HIPPOCRATES PARADOX"?

PUÒ L'ESPRESSIONE DELL'HSP60 E DELL'HSP10 DURANTE LA CANCEROGENESI BRONCHIALE CONFERMARE IL "PARADOSSO DI IPPOCRATE"?

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Abstract: Hsp60 and Hsp10 expression alteration may be directly or indirectly related to arise and/or progression of lung diseases. Indeed, we already demonstrated that the loss of their protective effects may drive bronchial epithelium towards cancer. We now hypothesise that a similar alteration may contribute to impairment of immunological responses in the more severe forms of chronic obstructive lung diseases, having thus a role in the progression of this disease.

KEY WORDS: Chaperonins, chronic inflammatory lung disease, bronchial cancer.

Abstract: Una alterazione della regolazione dell'espressione dell'Hsp60 e dell'Hsp10 può direttamente o indirettamente essere alla base dell'insorgenza e della progressione di patologie polmonari. Abbiamo già mostrato infatti che la perdita della loro funzione protettiva può condurre l'epitelio bronchiale normale a divenire tumorale. Ipotizziamo ora che una medesima alterazione può contribuire ad alterare la risposta immunologica nelle forme più severe di broncopneumopatia cronica ostruttiva, avendo quindi un ruolo nella progressione della malattia.

PAROLE CHIAVE: Chaperonine, malattie infiammatorie croniche del polmone, carcinoma broncogeno.

Recently Wheeler and Wong (W&W) described how the expression of Heat Shock Proteins (Hsps) may grow in response to a variety of stressors. In particular, they focused on the fact that the expression of some Hsps, like Hsp27, Hsp32, Hsp60 and Hsp70, may be upregulated possibly as a cytoprotective response stimulated by danger signals during acute lung disease [1].
Concerning Hsp60, the Authors report that many factors induce the overexpression of this gene, like ozone and heavy metals exposure, concluding that Hsp60 confers stress tolerance in the lung, like in other organs. Concerning this hypothesis, we here report some our recent clinical studies which extend the notions presented by W&W, demonstrating a wider spectrum of actions for these chaperonins.
Hsp60 and its co-chaperonin Hsp10 work closely together in mitochondria and other cellular compartments to confer the three-dimensional structure to proteins and to stabilize cytoskeletric and cytoplasmic proteins. Both are overexpressed during carcinogenesis of large bowel [2,3,4], uterine exocervix [4,5], prostate [6], oesophagus [7] and ovary [8], while their expression did not change significantly in myelodysplasia and during breast cancer development (our unpublished data). By contrast, in at least two anatomical districts, specifically urinary bladder [9,10] and airway [11,12], they may be downregulated.
In particular, in a recent work [12], we found that the development and progression of bronchial cancer in smokers with Chronic Obstructive Pulmonary Disease (COPD) is related to the loss of Hsp60 and Hsp10 immunopositivity. It is known that COPD patients develop a chronic inflammatory response involving peripheral and central airways [13]. As W&W reported, Hsp60 may activate the immunitary re-

sponse during inflammation, resulting in dendritic cell (DC) activation and maturation, and release of proinflammatory cytokines. DCs are reported to be decreased in tobacco smoke exposed mice [14] and neutrophil elastase from COPD patients sputa inhibited DC maturation and functions impairing the normal immune response in these patients [15]. It is also well known that DCs activation may contribute to limit tumoral progression in breast [16], oesophagus [17], and other organs. We already postulated that a clinical positive response can be recognised during COPD progression until the immunitary system remains responsive and capable to orchestrate a cellular mediated response devoted to lung repair [13]. It has been also previously reported a downregulation of CD3+ cells coexpressing CCR5 receptor (mainly expressed on T cells producing IFNγ) in severe COPD patients compared to mild COPD and control smoking subjects [18]. Moreover, Hsp60 may induce CCR5 overexpression by CD3+ cells, while oral administration of human Hsp60 recombinant DNA vaccine was associated with a decreased expression of CCR5+ Th1 and with a better control of clinical manifestations in patients with Behcet's disease [19] and adjuvant arthritis [20].

So that, Hsp60 stimulation of DCs and orchestration of a Tc1 positive response in smokers with COPD or other diseases having a prominent Tc1 inflammatory response, can be considered part of the cellular and molecular control for an adequate and effective immunological response, while in contrast, its disregulation may promote disease progression. Unfortunately, at present Hsp60 and Hsp10 have not jet been investigated in the progression of COPD, but we are working on that. Nevertheless, we have already observed that alterations of some of these mechanisms, such as downregulation of Hsp60 and Hsp10 at epithelial level, may start the imbalance conducting to a disregulation of the immunitary response and ultimately to lung cancer development in patients suffering from COPD [12].

We then conclude postulating that disregulation of Hsp60 and Hsp10 proteins could be (directly or indirectly) related to manifestations or to progression of lung diseases. In fact, the loss of their protective effects may drive bronchial epithelium towards cancer. Moreover, we hypothesise that it may contribute to impairment of immunological responses in the more severe forms of COPD playing a role in the progression of this disease. Nevertheless, further investigations are necessaries to better address the role of these Hsps in both acute and chronic lung injuries. Paraphrasing the phrase of Hippocrates that W&W reported at the beginning of their review, "That which drug and scalpels cannot cure, *heat shock proteins* (Nature?) may cure, alternatively it must be determined to be incurable".

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