ABSTRACT BOOK

01 Patogenesi ed interazioni microrganismo-ospite

25 - Targeting PAD-mediated citrullination to treat human papillomavirus infections

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INTRODUCTION: Human Papillomaviruses (HPVs) are oncogenic DNA viruses that infect mucosal or cutaneous epithelia inducing cell proliferation. While most HPV types, referred as low-risk, produce mild benign pathogenic effects, a part of HPV types, called high-risk, may lead to cancer. Citrullination is an emerging post-translational modification catalyzed by peptidyl arginine deiminases (PADs) that convert peptidylarginine into peptidylcitrulline. In humans, the PAD family is composed of five isozymes (PADs 1-4, 6), ubiquitously expressed, and relevant to human diseases, including cancer.
MATERIALS AND METHODS: To characterize the molecular mechanisms regulating HPV-induced protein citrullination, we took advantage of different *in vitro* models of persistent, high-risk, HPV infections, *i.e.* HeLa and CaSki cells, containing integrated copies of HPV18 and HPV16, respectively.
RESULTS: We demonstrated that the expression of E6 and E7 HPV oncoproteins is strongly impaired in the presence of the pan-PAD inhibitor BB-Cl-amidine, as well as upon treatment with specific PAD-inhibitors (GSK-199, AFM30), indicating that citrullination is required for HPV pathogenesis. Consistently, p53 and p21, the main targets of HPV oncoproteins, are upregulated by PAD inhibitors. The overall citrullination nor the PADs profile are affected by E6 and E7 expression *in vitro*, but preliminary *in vivo* analyses revealed a significant association between PAD4 expression and cervical cancer progression.
DISCUSSION AND CONCLUSIONS: These findings could provide new insights into novel pathways elicited by high-risk HPV infection, which will constitute the rationale for the design of small molecule inhibitors able to block the specific factors responsible for PAD transactivation.