Targeting cytosolic proliferating cell nuclear antigen in neutrophil-dominated inflammation.

New therapeutic approaches that can accelerate neutrophil apoptosis under inflammatory conditions to enhance the resolution of inflammation are now under study. Neutrophils are deprived of proliferative capacity and have a tightly controlled lifespan to avoid their persistence at the site of injury. We have recently described that the proliferating cell nuclear antigen (PCNA), a nuclear factor involved in DNA replication and repair of proliferating cells is a key regulator of neutrophil survival. The nuclear-to-cytoplasmic relocalization occurred during granulocytic differentiation and is dependent on a nuclear export sequence thus strongly suggesting that PCNA has physiologic cytoplasmic functions. In this review, we will try to put into perspective the physiologic relevance of PCNA in neutrophils. We will discuss key issues such as molecular structure, post-translational modifications, based on our knowledge of nuclear PCNA, assuming that similar principles governing its function are conserved between nuclear and cytosolic PCNA. The example of cystic fibrosis that features one of the most intense neutrophil-dominated pulmonary inflammation will be discussed. We believe that through an intimate comprehension of the cytosolic PCNA scaffold based on nuclear PCNA knowledge, novel pathways regulating neutrophil survival can be unraveled and innovative agents can be developed to dampen inflammation where it proves detrimental.
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