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PKC epsilon/PKC delta rate regulates human platelets production

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Platelet production is the terminal step of the megakaryocytopoiesis process (1). We previously observed that PKCepsilon, a member of the Protein Kinase C family of serine/threonine kinases, expression varies during human MK differentiation and modulates MK maturation and platelet release (2). Besides, it is also critical for proplatelet formation in murine model (3). Here we utilized an *in vitro* model of human platelet production to investigate a potential role for PKCdelta, well known to mediate contrasting and even opposing effects as compared to PKCepsilon in several non-hematopoietic models (4), in MK differentiation and proplatelet formation. By western blot analysis we found that PKCdelta expression escalates during megakarocyte differentiation and remains elevated during the final step of this process, with an opposite kinetics as compared to PKCepsilon expression levels. Furthermore, by using specific shRNA we observed that PKCdelta inhibition affected both MK differentiation, in terms of cell survival and ploidy, and platelet production. The correlation between PKCdelta/PKCepsilon levels and MK differentiation was also confirmed by pathological models. Indeed, primary myelofibrosis (PMF), characterized by an impaired MK differentiation, showed higher levels of PKCepsilon and reduced expression of PKCdelta. On the contrary, in essential thrombocytemia (ET), featured by a physiological increase of platelet number, PKCepsilon is virtually absent and PKCdelta is well represented. Finally, we demonstrated that the concurrent pharmacological inhibition of PKCepsilon and activation of PKCdelta are capable to build up platelet production in human. Collectively, these data indicate that novel PKCs are critical mediator of human proplatelet formation and the modulation of their expression might be a future strategy to revise platelet production.

References:

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Keywords

Novel PKC; platelet; thrombopoiesis.