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Platelets as key players in the dynamic interplay of inflammation and immunity in atherothrombosis and cancer: highlighting new opportunities for preventive strategies

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Short summary:

Inflammation plays a critical role in the pathogenesis of various diseases by promoting the acquisition of new functional traits by different cell types. Shared risk factors between cardiovascular disease and cancer, including smoking, obesity, diabetes, high-fat diet, low physical activity, and alcohol consumption, contribute to inflammation linked to platelet activation. Platelets contribute to an inflammatory state by activating various normal cells, such as fibroblasts, immune cells, and vascular cells. This activation is achieved by releasing diverse molecules from platelets, including lipids (eicosanoids), growth and angiogenic factors, and extracellular vesicles(EVs) rich in various RNA species. Antiplatelet agents like low-dose aspirin can prevent cardiovascular disease and cancer by inhibiting platelet functions beyond the antithrombotic action. Notably, platelets induce the epithelial-mesenchymal transition(EMT) in tumor cells, enhancing their metastatic potential. Two platelet eicosanoids, PGE_2 (generated as a minor product of COX-1) and 12S-hydroxyeicosatetraenoic acid(HETE) [derived from the platelet-type 12-

lipoxygenase(LOX)], contribute to EMT. In addition to the pharmacological inhibition of eicosanoid biosynthesis, a potential strategy for mitigating platelet-induced metastasis might encompass the inhibition of direct interactions between platelets and cancer cells. New antiplatelet drugs, such as revacept and selective 12-LOX inhibitors, currently under clinical development, are of interest due to their low risk of bleeding. Platelets and EVs carry important clinical information because they contain specific proteins and RNAs associated with disease conditions. Their analysis can improve the accuracy of liquid biopsies for early disease detection, monitoring progression, and assessing drug response.

In the current era of precision medicine, developing treatment protocols involving the safe utilization of antiplatelet agents to prevent cancer and cardiovascular disease necessitates adopting a systems biology approach. This strategy entails a comprehensive analysis of heterogeneous datasets, including genomics, epigenomics, proteomics, lipidomics, and clinical data, at the level of the individual patient. This procedure involves dynamic systems modeling to identify candidate pathways contributing to aspirin's benefits and harms and possibly other antiplatelet agents. Additionally, this strategy will help identify susceptibility profiles for disease, verifying whether platelet- and EV-based liquid biopsy can predict the onset and recurrence of cancer and atherothrombosis.

Biosketch:

Paola Patrignani is a Full Professor of Pharmacology at "G. d'Annunzio" University, Department of Neuroscience, Imaging and Clinical Sciences, Chieti, Italy. She is heading the Laboratory of Systems Pharmacology and Translational Therapeutics (SPaTT Lab) at the Center for Advanced Studies and Technology (CAST). She worked for two years as a Postdoctoral Research Fellow at the Laval University Hospital (Quebec, Canada) and the Department of Pharmacology of Merck Frosst (Kirkland, Quebec, Canada). In 2009, she was a Visiting Professor at the Goethe University Frankfurt am Main (Germany). He is a member of the Italian Society of Pharmacology, Societŕ Italiana per lo studio dell’Emostasi e Thrombos (SISET) and International Society of Thrombosis and Hemostasis (ISTH). She worked as an evaluator for EIC Pathfinder 2024, a funding program under Horizon Europe, and referee of many International and National Research Agency: the Health Research Board (HRB) of Ireland; the Wellcome Trust, Yorkshire Cancer Research Awards (UK);"Laboratories of

excellence" - ANR (French Research Funding Agency); American Heart Association Grants; British Heart Foundation; Cancer Research UK; WCRF International grant program (UK), National Science Centre (Poland); PRIN, FIRB, SIR, VQR 2004-2010, VQR 2011-2014. She has won the International Aspirin Foundation Senior Science Award 2018. In 2013 she received a special prize from the Committee for the Promotion of Women's Entrepreneurship in the Abruzzo Region (Italy). She is one of the Top Italian Women Scientists (TIWS) who announce Italian science with high-profile publications. She is listed among the world's top 2% of scientists in the “Updated science-wide author databases of standardized citation indicators,” published on 4 October 2023 by Stanford University (US). She is the Editor in Chief of Frontiers in Inflammation Pharmacology and on the Editorial Board of two journals of the American Society for Clinical Pharmacology & Therapeutics: Clinical Pharmacology and Therapeutics and Clinical and Translational Science (CTS). Her scientific activity is documented by 200 publications in international journals ranked in the Journal Citation Reports (total citations: 17664, H-index:67) and more than 20 chapters in international textbooks. She is the inventor of 6 patents (3 Italian, 2 European, and 1 in the USA).

Prof. Patrignani's research focuses on eicosanoids in cardiovascular disease (CVD) and cancer by pursuing interdisciplinary translational science on therapeutics and biomarker discovery for precision medicine. Her groundbreaking research covers a broad spectrum of areas, including 3D cell cultures, genetically modified mice, and clinical pharmacology. Her tireless efforts have advanced our knowledge and brought us closer to discovering new treatments for life-threatening diseases, such as myocardial infarction and cancer. In the last 10 years, Paola Patrignani received several national and international research grants as principal investigator (PI) (PRIN 2010FHH32M, AIRC-IG12111; Aragon Institute Health Sciences (IACS), Zaragoza, Spain (Research Agreement), AIRC-IG20365) and as co-PI (AsCaP Collaboration Funded by Cancer Research UK, CRUK). She also received grants from pharmaceutical companies such as Dompé (Italy) and Innovate Pharmaceuticals (Manchester, UK).

Relevant publications:

Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials.
N Bhala, J Emberson, A Merhi, S Abramson, N Arber, JA Baron, ...
Lancet (London, England) 382 (9894), 769-779

Selective cumulative inhibition of platelet thromboxane production by low-dose aspirin in healthy subjects
P Patrignani, P Filabozzi, C Patrono
The Journal of clinical investigation 69 (6), 1366-1372 1

Biochemical and pharmacological characterization of the cyclooxygenase activity of human blood prostaglandin endoperoxide synthases.
P Patrignani, MR Panara, A Greco, O Fusco, C Natoli, S Iacobelli, ...
Journal of Pharmacology and Experimental Therapeutics 271 (3), 1705-1712

New insights into the use of currently available non-steroidal anti-inflammatory drugs
K Brune, P Patrignani
Journal of pain research, 105-118

Clinical pharmacology of platelet cyclooxygenase inhibition.
C Patrono, G Ciabattoni, P Patrignani, F Pugliese, P Filabozzi, F Catella, ...
Circulation 72 (6), 1177-1184

Advances in NSAID development: evolution of diclofenac products using pharmaceutical technology
R Altman, B Bosch, K Brune, P Patrignani, C Young
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