Determination of targets for peptidylarginine deiminase type 4 (PAD4) among complement system proteins and assessment of citrullination influence on their biological activity.

The presence of inflammation is a natural consequence of minor injuries, infections as well as chronic diseases. It is developed by the activation of host defense mechanisms, in which the complement system (CS) plays a vital role. CS is a part of our innate immunity and its activation occures in response to the presence of invading pathogens. However, the function of CS is not limited to the protection against invading microbes. Equally important is its capability of labeling the apoptotic and necrotic cells and its fragments for effective clearance, preventing the autoimmune response development from such debris, as well as its immunomodulatory potential in regulating the state of inflammation. Proper functioning of this system is crucial in maintaining the homeostasis. Any kind of deregulation due to internal or external factors (resulting in overactivity or in weakened activity) may affect the development of more serious health conditions, as was previously described on different stages of pathogenesis of diseases such as rheumatoid arthritis, systemic lupus erythematosus or cancer.

Another characteristic event within the inflammation state is the infiltration of the inflamed tissue by the immune cells like neutrophils or macrophages. Such an event might be the source of deiminase activity due to the release of enzyme peptidylarginine deimanse 4 (PAD4), physiologically present only intracellularly, from the dying cells or during neutrophil extracellular trap formation (NETosis). Posttranslational modification catalyzed by PAD4, citrullination (modification of arginine residues to citrulline within peptide chains), may potentially affect any protein present in enzyme surroundings, thus leading to changes in a protein's secondary or tertiary structure, function and interaction with their physiological partners. So far *in vitro* and *in vivo* studies allowed for recognition of several PAD4's targets comprising of the structural proteins (collagen, fibrin, filagrin), transcription factors, antimicrobial peptide LL-37, chemokines and protease inhibitors from serpins family, all described in the event of a pathological state such as prolonged inflammation. Interestingly, except for the influence on biological activity of proteins, modification by PADs results in formation of neoepitopes triggering autoimmune responses as it occurs in RA.

Due to the presence of both CS proteins and PAD4 in the same microenvironment during inflammatory states and the significant role played by citrullination in the pathological conditions mentioned above, we will delineate the potential of this deiminase to modify CS components as well as describe the effects of this modification on their biological activity. This proposal will broaden the knowledge about contribution of CS and PAD4 in the regulation of inflammatory processes and disease development not only from the perspective of potential changes in CS components activity upon citrullination but also in case of possible triggering of autoimmune response against such modified proteins. This will allow for better understanding of the pathological mechanisms observed in chronic inflammation and autoimmune diseases and may pave way for novel therapeutic strategies.