Lectures


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L13. Apoptosis, Apoptotic cell clearance and resolution of inflammation

The resolution of inflammation is increasingly being recognised as an active and manipulatable phenomenon that could lead to the identification of novel therapeutic targets for the treatment of both acute and chronic inflammatory diseases [1–5]. Inflammatory leukocytes, especially granulocytes and macrophages, have evolved to be efficient cells for host defence in the fight against continuous invasion by organisms such as bacteria, parasites, fungi and viruses. However, excessive leukocyte accumulation, dysregulated leukocyte activation and/or failed clearance of effete cells will result in cellular and tissue damage occurring in tissues affected by chronic inflammatory diseases (e.g. vasculitis, rheumatoid arthritis, bronchitis, inflammatory bowel disease, cardiovascular disease, etc.) [6–10]. The recent focus, by my group and others, on the processes and mechanisms governing the resolution of inflammation has identified new potential pharmacological intervention strategies. The process of catabasis, defined as a return to normal cellular and tissue homeostasis, during an episode of inflammation involves the active process of resolution. The cellular processes occurring during inflammation resolution include a form of programmed cell death commonly referred to as apoptosis and non-phlogistic phagocytosis of apoptotic cells by phagocytes (e.g. macrophages and dendritic cells) often called efferocytosis [1–5]. These processes, if executed in controlled fashion, result in attenuation of inflammation as a consequence of:

• termination of inflammatory cell responsiveness occurring during apoptosis and;
• the phagocytosing cells changing from a pro-inflammatory to a more anti-inflammatory or pro-resolution phenotype.

Thus, pharmacological interventions which induce granulocyte (neutrophil or eosinophil) apoptosis resulting in non-inflammatory macrophage efferocytosis is an attractive therapeutic strategy [5,11]. An example of such an approach includes evidence derived from in vitro human cellular work and animal (mouse and zebrafish) in vivo experiments showing that cyclin-dependent kinase (CDK) inhibitor drugs promote resolution of inflammation. These drugs, which are under development and undergoing clinical trials for a variety of cancers, induce profound concentration- and time-dependent human neutrophil and eosinophil apoptosis [12–14]. Importantly however, when CDK inhibitor drugs are administered once inflammation has been established in a variety of mouse models, they drive caspase-dependent granulocyte apoptosis to promote inflammation resolution [12,14,15]. The specific molecular mechan-
isms of how these drugs exert their pro-resolution properties is under intense investigation and it has been proposed that inhibition of specific CDKs (e.g. CDK9) by these drugs results in down-regulation of transcription by limiting RNA polymerase II activity [15,16]. Evidence indicates that CDK inhibitor drugs (and other compounds, e.g. flavones [17]) result in down-regulation of key anti-apoptotic proteins such as the Bcl-2 family member Mcl-1 to drive apoptosis to promote resolution [12–18]. Other agents that promote resolution include the pro-resolution lipids (e.g. lipoxins, resolvins and maresins) [1,2], cytokines (especially IL-10) [19] and glucocorticosteroids [20]. These molecules, like CDK inhibitor drugs, skew inflammatory processes towards resolution by influencing inflammatory cell apoptosis and/or efferocytosis. It is believed that future therapies for acute and chronic inflammatory diseases will be developed from a directed strategy to deliberately influence pro-resolution mechanisms and processes.

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References

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L14. Immunomodulatory properties of apoptotic cells

Introduction
Chronic inflammation usually originates from a dysfunction in tolerance processes implicating a variety of soluble factors and immune cells. In homeostatic conditions, an inflammatory event triggering by, for instance, pathogen invasion, necrotic damaged cells or irritants is a natural process initiated to protect