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Nanomedicine: Will it be able to overcome multidrug resistance in cancers?

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At present, every third individual in the Western world is diagnosed with a cancer at some point in their lives. In spite of great advances in oncology in recent decades, around 50% of these individuals will die from their diseases. The great majority of these deaths are caused by cancer cells endowed with multiple drug resistance (MDR). These cells are not eliminated by present-day therapies and new strategies for general oncologic treatment are needed. The shape of such new treatments is emerging and such treatments will likely be highly individualized but at the same time highly complex and costly. Multimodality is mandatory and the treatment steps will be sequential. The plausible major steps are likely to be: Blocking of the genes responsible for MDR; killing of the adult cancer cells that are protecting the malignant stem cells. With the genes blocked in step 1, the adult cancer cells will be more susceptible to toxic drugs. This will allow smaller amounts of therapeutic drugs to be used, leading to fewer toxic side effects; the dead adult cancer cells must be removed to expose the dormant cancer stem cells. Dormant cancer cells are believed to be unaffected by present-day oncologic therapies; initiation of proliferation among the cancer stem cells which will make them susceptible to education or killing; and killing of the malignant stem cells or educating them to enter permanent dormancy and thus render them harmless. For these five steps, the medical profession is already in possession of most of the needed therapeutic agents. However, some of these agents are toxic when given intravenously in humans and some of them are inactivated during the transport in the blood. Nanoparticles might offer a dual benefit by protecting the patient from the agent and simultaneously protecting the agent from the patient. What is lacking is knowledge of the time needed for each step and of the potential side effects for each step. Effective targeting methods currently exist for superficial tumors (both primary and secondary) but not for deep-seated cancers.

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The *TLR4-SOCS1-p38MAPK* axis regulates macrophage polarization in response to lipopolysaccharide

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Activated macrophages regulate the course, locality, duration and severity of inflammation. During the course of inflammation, distinct macrophage phenotypes have been observed. M1-macrophages are believed to be involved in the initiation and propagation of inflammation while M2 macrophages are apparently involved in the resolution of the inflammatory process. Therefore, identifying the regulatory mechanisms of macrophage phenotypic specification can be useful clinically to mitigate tissue damage and foment repair caused by dysregulated or persistent inflammatory conditions. Here we show that NOS1 regulation of suppressor of cytokine signaling-1 (SOCS1) stability in macrophages as a critical effector of macrophage phenotypic specification thereby indicating that NOS1 may be a clinically relevant drug target to suppress chronic inflammatory conditions. Further, increased amounts of SOCS1 in NOS1-/- macrophages leads to decreased p38MAPK activity, which impairs expression of M1 signature markers but not M1 genes. These data illustrate the molecular checkpoints involved in homeostatic macrophage polarization and suggest new therapeutic strategies to prevent inflammatory responses.

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