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A Historical and Evolutionary Perspective on Circulating Nucleic Acids and Extracellular Vesicles: Circulating Nucleic Acids as Homeostatic Genetic Entities

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Abstract

The quantitative and qualitative differences of circulating nucleic acids (cirNAs) between healthy and diseased individuals have motivated researchers to utilize these differences in the diagnosis and prognosis of various pathologies. The position maintained here is that reviewing the rather neglected early work associated with cirNAs and extracellular vesicles (EVs) is required to fully describe the nature of cirNAs. This review consists of an empirically up-to-date schematic summary of the major events that developed and integrated the concepts of heredity, genetic information and cirNAs. This reveals a clear pattern implicating cirNA as a homeostatic entity or messenger of genetic information. The schematic summary paints a picture of how cirNAs may serve as homeostatic genetic entities that promote synchrony of both adaptation and damage in tissues and organs depending on the source of the message.

Keywords

Circulating nucleic acids • Extracellular vesicles • Genetic homeostasis • Metabolic DNA • Bystander effect • Genometastasis

Introduction

Since the discovery of cirNAs in human plasma in 1948, there has been considerable amount of research regarding their diagnostic applications (Fleischhacker and Schmidt 2007). Despite the progress made, there are still inconsistencies that bolster clinical application and this is mainly due to a lack of standard operating procedures in the storage, extraction and processing of cirNAs. However, our lack of knowledge regarding the origin and purpose of cirNAs is an equal culprit. The aim of this review is to illustrate the development of cirNA research in order to elucidate cirNA as homeostatic entities or messengers of genetic information. The

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Homeostasis and DNA

DNA is vulnerable to change or damage, especially during transcription and replication. These processes are highly regulated to prevent errors from occurring, but changes can still occur and our living environment provides additional challenges to genome integrity. If all other body functions utilize homeostatic functions to maintain stability and balance, is it possible that there can be some form of homeostatic regulation for genetic information?

In 1954 Michael Lerner coined the term "genetic homeostasis", referring to the ability of a population of organisms to equilibrate its genetic composition and to resist sudden changes (Hall 2005). As the term stands, it is not really applicable to the article's aim, unless one refers to different organs, tissues and cell types as populations within the body of an organism. As with populations of organisms, genetic changes do not always occur uniformly throughout the organs and tissues of the body, but in most cases begin as isolated incidences. These changes, however, can spread to and affect nearby cells and tissues. Take the bystander effect, for example, which refers to the effect of information transfer from targeted cells exposed to damaging agents of a physical or chemical nature to adjacent cells (Ermakov et al. 2013). Targeted UV irradiation results in the release of clastogenic factors by irradiated cells that can induce apoptosis and necrosis in adjacent non-irradiated cells. These clastogenic factors have been identified as extracellular DNA (Ermakov et al. 2011) and their effects have also been found to persist in the progeny of irradiated cells that survived irradiation (Seymour and Mothersill 2000).

The Four Paradigms of the History and Development of cirNAs and EVs

The question now is whether cirNAs can serve as homeostatic entities or messengers to promote stability and equilibrium of genetic data among a population of tissues/organs. We believe this is the case and there are several instances in the discovery and development of cirNAs and extracellular vesicles (EVs) that strongly indicate this. The history and development of cirNAs and EVs consist of four main topics or paradigms, namely heredity, DNA, messengers and the cirNAs and EVs (see Fig. 17.1).

Conclusions

To conclude we ask again, can cirNAs serve as homeostatic entities or messengers to promote stability and equilibrium of genetic data among a population of tissues or organs? The answer is yes. According to our empirically up-to-date schematic summary of the history and development of cirNA research and the contributions of EV research:

(i) Darwin coined the idea of free moving updated data particles originating from all tissues;
(ii) Griffith and Avery showed us that these particles are nucleic acids and can transfer beneficial information from one place to another and can be inherited;
(iii) De Vries, Bell, Stroun, Pelc, Anker and Gahan showed us that these particles are not necessarily for heredity, but to convey messages;
(iv) Pelc showed us that metabolic DNA, and therefore spontaneously released DNA or virtosomes (if metabolic DNA serves as

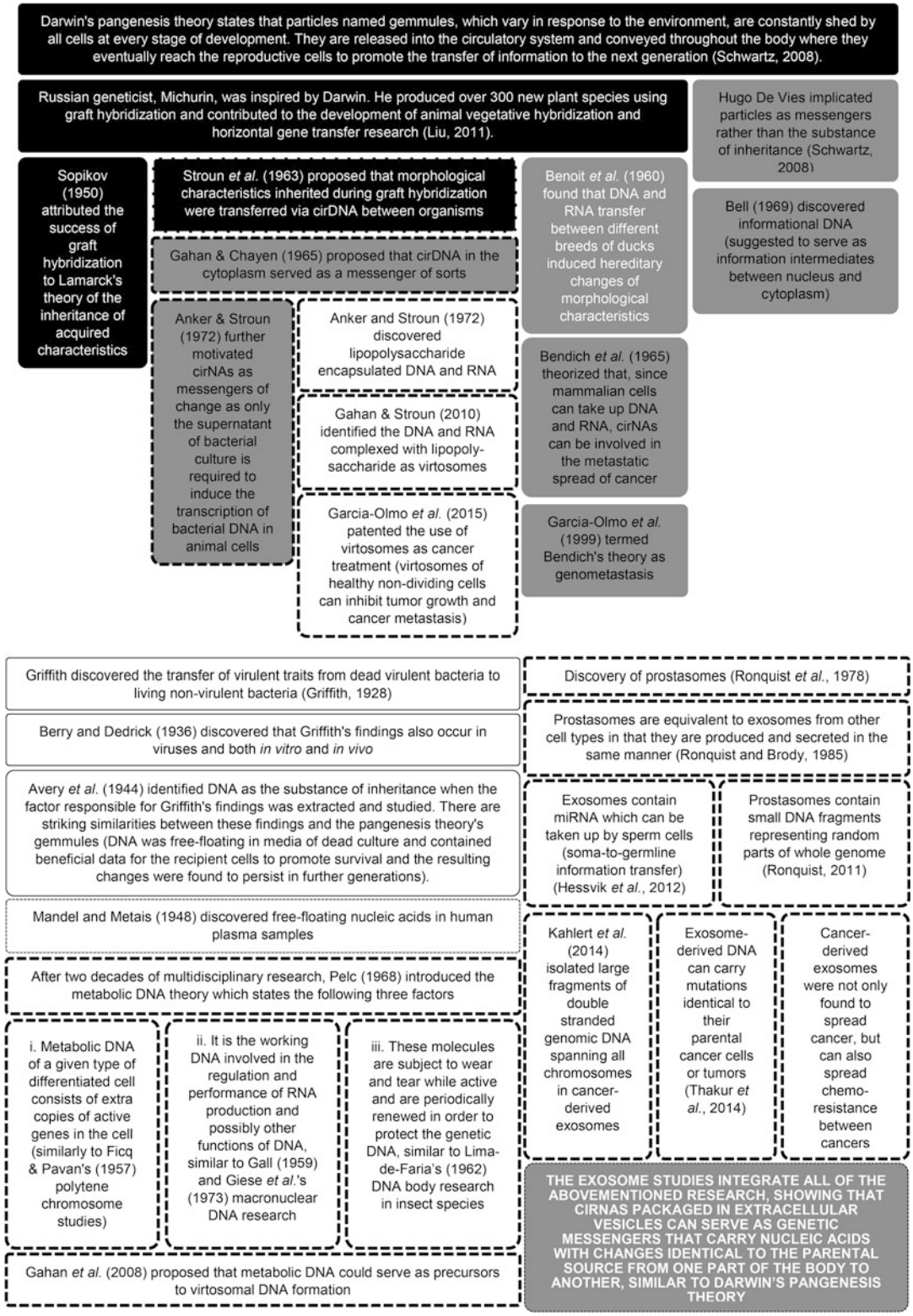

Fig. 17.1 Empirically up-to-date schematic summary of a few of the major events that developed and integrated the concepts of heredity, genetic information, cirNAs and EVs. The relationships of the four paradigms of cirNA research are illustrated: Heredity (*black* with *white font*), DNA research (*white*), messengers (*dark grey* with *black font*) and cirNA and EV research (*dash lines*). Areas with other combinations of *dash lines* and *fonts* represent data that fall under more than one of the four categories

their precursors), are separate entities from our genetic DNA;

(v) The transcession studies and subsequent genometastasis and exosome research showed us that cirNA release becomes prominent when change occurs (e.g. bacterial exposure leading to transcription of bacterial DNA into recipient cells, cancer mutations, epigenetic changes, damage and/or repair due to stressors such as irradiation exposure);

(vi) CirNAs contain the changes or mutations of the parent tissue;

(vii) Garcia-Olmo's patent showed us that it is not only cirNAs related to diseases, disorders and/or damage that can induce change;

(viii) Genometastasis and the bystander effect showed us that these cirNAs can transfer change from one place to another and can become persistent in following generations. CirNas could, therefore via horizontal gene transfer, serve as homeostatic entities or messengers of genetic information.

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Conflict of Interest The authors declare no conflict of interest.

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